Assessing the Potential Effects of a Flavored Tobacco Product Ban to Inform FDA Decision-Making: A systematic review, decision analysis and economic evaluation

by
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ABSTRACT

Introduction: The purpose of this dissertation is to synthesize and translate research on flavored tobacco in the United States in order to inform regulatory decision-making at the U.S. Food and Drug Administration. Three related manuscripts aim to: 1) synthesize existing research examining the use and attitudes/knowledge/perceptions of flavored tobacco in the United States, specifically focusing on how age and nonflavored tobacco use are correlated with flavored tobacco use; 2) estimate the relative health effects, compared to the status quo, that would be expected to result from a) a ban on combustible flavored tobacco products and b) a ban on all flavored tobacco products, and organize existing relevant research that informs the policy decision; and 3) determine acceptable ceiling costs for the policies considered in the second aim, and identify the minimum effectiveness levels at which these interventions would be considered cost-effective and cost-saving.

Methods: We used a systematic review to achieve the first aim, and conducted a qualitative synthesis for included studies. To achieve the second aim, we developed a decision tree using TreeAge Pro 2014. This model compared three policy options: 1) the banning of all flavored combustible tobacco products, 2) the banning of all flavored tobacco products (inclusive of combustible and smokeless products), and 3) the status quo, in which only flavored cigarettes are banned. To achieve the third aim, we performed a threshold analyses to establish cost and performance standards for the policy options considered in the second aim. Microsoft Excel 2011 was used for this analysis.

Results: The results of the systematic review highlight the association between flavored tobacco use and young age, and suggest that flavoring may promote tobacco use in adolescent and young adult populations. The second manuscript, which examined the policy options among a young adult population, found that a ban on all flavored tobacco products would likely produce the most favorable outcome of the policy options considered. This finding is contingent upon the validity of the model's underlying structural assumptions, as well as assumptions that determined the model's parameter values. The results of the cost threshold analysis indicated that the cost of either policy option would need to reach well into the multi-billion dollar range in order for society to deem the cost of either of the policies to be unacceptable. The results of the effectiveness threshold analysis found that both policy options would be cost-effective if less than 1% of the expected number of averted adults smokers were actually averted. As with the model developed for the second manuscript, the parameter values used to conduct the threshold analyses were subject to uncertainty.

Conclusions: The results of this dissertation speak to the FDA's request for information and data to support the establishment of a product standard prohibiting flavors in at least some noncigarette tobacco products. The studies described here can be thought of as exploratory analyses that can be built upon and adapted to directly answer questions posed by the FDA. The model presented in the second manuscript, in particular, could be used to address a range of regulatory options, as it provides a general framework for considering the impact of policies intended to reduce the attractiveness of tobacco products, while taking into consideration the varying levels of risk presented by different

products. Additional research should be conducted to inform the development of a more complex model that can provide additional insight into the effects of implementing the policies considered in this dissertation, as well as other regulatory options.

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Chapter 1 - INTRODUCTION

The health and economic consequences of tobacco use in the United States are substantial. Tobacco use is the primary preventable cause of premature morbidity and mortality (1). Between 2005-2009, cigarette use was responsible for at least 480,000 annual premature deaths (1), and approximately 8.6 million individuals experienced serious smoking-attributable medical conditions in the year 2000 (2). These estimates do not include morbidity or mortality caused by the use of other forms of tobacco. Economically, smoking-attributable health care expenditures were estimated to be $175.9 billion in 2013 (1). From 2005-2009, smoking-attributable premature death cost approximately $107.6 billion due to losses in productivity (1).

The detrimental health effects of cigarette use have been widely acknowledged since the 1960s, during which the Surgeon General released the first report on smoking and health (3). Since that time, researchers have identified an increasing number of diseases with which tobacco use is causally linked, including multiple forms of cancer and chronic obstructive pulmonary disease (1).

Tobacco control legislation in the United States

Despite knowledge of the negative health consequences of tobacco use, efforts to minimize the burden inflicted by tobacco use were initially limited. The Federal Cigarette Labeling and Advertising Act of 1965 and the Public Health Cigarette Smoking Act of

1969 restricted cigarette advertising on radio and television programs, required that cigarette packages bear a health warning label, and called for an annual update on the health effects of smoking (3). The next large-scale restrictions imposed upon the tobacco industry resulted from the Master Settlement Agreement of 1998, in which the Attorneys General of 46 states sued the five largest tobacco companies in the United States (4). Provisions of the agreement forbade the industry from directly or indirectly targeting advertisements or marketing towards youth, and they imposed other prohibitions around marketing and advertising, including bans on outdoor advertising and the use of cartoon characters (4). These measures proved to be inadequate, as well over a fifth of adults and students continued to use tobacco in the early years of the 21st century (5).

In order to address the continued contribution of tobacco use to morbidity and mortality in the U.S., in June of 2009, President Obama signed the Family Smoking Prevention and Tobacco Control Act (FSPTCA) into law. The FSPTCA grants the U.S. Food and Drug Administration (FDA) authority to regulate the manufacturing, marketing and sale of tobacco products. A notable provision of the FSPTCA is that the FDA must issue tobacco regulations that are "appropriate for the protection of the public health" (6). In contrast to the individual-level "safe and effective" standard that FDA-regulated products are traditionally required to meet, this "public health standard" allows the FDA to consider the population-level effects of tobacco products when enacting regulatory decisions (7).

Regulation of flavored tobacco products

In Section 907 of the FSPTCA, cigarettes with characterizing flavors such as cherry, vanilla and grape were banned (6). The FSPTCA specifically states that

> …a cigarette or any of its component parts (including the tobacco, filter, or paper) shall not contain, as a constituent (including a smoke constituent) or additive, an artificial or natural flavor (other than tobacco or menthol) or an herb or spice, including strawberry, grape, orange, clove, cinnamon, pineapple, vanilla, coconut, licorice, cocoa, chocolate, cherry, or coffee, that is a characterizing flavor of the tobacco product or tobacco smoke (6).

The term "characterizing flavor" is not explicitly defined in the FSPTCA. That is, there is no quantitative level that defines how much flavor or menthol needs to be in a product in order for it to be a "characterizing" trait. The term "additive" is defined, albeit loosely, as "any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristic of any tobacco product" (6). Although the term "characterizing flavor" is not explicitly defined, the FSPTCA does not restrict the FDA's ability to take action applicable to menthol or other flavors, herbs or species not specified in Section 907 of the FSPTCA. The FDA has not provided a comprehensive list that specifies which products are illegal. Researchers conducting work related to flavored or menthol tobacco typically rely on brand designations to define what constitutes a flavored or menthol product (8).

No explicit justification was given for the exclusion of menthol products from the ban; this omission was likely made because mentholated cigarettes comprise a large share—approximately one third—of the cigarette market in the United States (9). While it can be argued that menthol is a type of flavor, because menthol was omitted from the flavored cigarette ban, the term "flavor" is typically understood not to include menthol in the

context of tobacco control policy. The manuscripts included in this dissertation will use these terms in a way that is consistent with tobacco control policy. "Flavored" products will be used to refer to products with characterizing flavors, excluding menthol.

In addition to excluding menthol products, the ban included in the FSPTCA did not apply to non-cigarette tobacco products. Under the FSPTCA, the FDA has authority to enact regulations impacting cigarettes and cigarette tobacco, roll-your-own tobacco, and smokeless tobacco products (6), with the option to regulate other tobacco products following the passage of a "deeming regulation," in which the FDA would specifically deem other products to fall under its authority. Thus, while smokeless tobacco products were excluded from the flavored product ban, the FDA does not currently possess the authority to extend the ban to other tobacco products.

The FDA's ability to enact a flavored tobacco ban for non-cigarette products, however, may soon change. In 2014, the FDA published a proposed ruling for the deeming regulation (10). While passage of the deeming regulation would not automatically extend the flavored tobacco ban to non-cigarette products, the proposed ruling indicates that the FDA would consider enacting such a regulation in the future, as it contains requests for comments and research on how to address flavored non-cigarette tobacco use (10).

Policy context

A number of governmental bodies in the U.S. and worldwide have implemented bans on flavored tobacco products. Domestically, New York City, New York and Providence,

Rhode Island passed laws that prohibit the sale of flavored non-cigarette tobacco products such as cigars, cigarillos and smokeless tobacco (11). Maine passed a law banning the sale of flavored cigar products, and Illinois passed a law banning the sale of flavored rolling paper and blunt wraps (11). Other countries such as Canada, Australia and Brazil have also taken actions to reduce the use of flavored tobacco products. In Canada, the sale of cigarettes, little cigars, cigarillos, and blunt wraps weighing 1.4g or less that contain most flavoring agents (excluding menthol) is prohibited (12). The sale of fruit- and candy-flavored cigarettes is banned in several Australian states (13). Flavorings, including menthol, in all tobacco products are banned in Brazil (14).

In addition to banning the sale of cigarettes with characterizing flavors, Section 907 of the FSPTCA allows the FDA to enact other standards for tobacco products, such as regulating tar and nicotine levels (6). However, the FDA is not allowed to reduce nicotine levels to zero, nor may it enact a ban on specific types of tobacco products (for example, the FDA may not ban all cigarettes, all smokeless tobacco or all little cigars) (6).

Tobacco use among young adults

The definition of a "young adult" varies across tobacco control studies conducted in the U.S., with age ranges spanning from 18-24 to 18-35 (15-20). In the context of this dissertation, "young adult" should be understood to encompass 18-34 year olds, unless otherwise noted. Conceptually, "young adulthood" refers to a stage in which individuals are developmentally and socially distinct from children and older adults (21).

Tobacco use patterns in young adult populations have become of increasing interest to researchers in recent years. Young adults represent the tobacco industry's youngest legal market in the U.S., and prevalence of tobacco products is especially high in this population (1, 22). The 2009-10 National Adult Tobacco Survey found that prevalence of products examined individually (cigarettes, cigars/cigarillos/small cigars, chew/snuff/dip, water pipes, snus) as well as use of any tobacco product decreased with increasing age, with prevalence highest among 18-24 year olds (22). Another study examining current use of multiple products found that rates of multiple product use were highest among 18-24 year olds and 24-34 year olds compared with older adults (1). Additionally, over the past decade, tobacco control researchers have found that, contrary to previous assumptions that tobacco use behaviors were established before the age of 18, young adulthood is an important stage during which tobacco use is initiated and solidified (17, 23, 24). Engaging in risk behaviors during this time may be considered socially acceptable and, thus, may facilitate the use of addictive substances such as tobacco (25, 26). As such, public health initiatives that focus on lowering initiation and increasing cessation among young adults can play an important role in lowering long-term morbidity and mortality rates. Recent research has focused on learning more about the unique patterns of tobacco use in this age group (17, 23, 24, 27).

Flavored tobacco use among young adults and FDA response

Data show that prevalence of flavored tobacco use is high among young adults and that it decreases with increasing age. A 2012 survey examining tobacco use among a nationally representative sample of young adults in the United States found that, among past 30-day

smokers, current flavored tobacco was 18.5% (95% CI: 15.2-22.2) (20). When examined by product, prevalence of flavored tobacco use was highest for hookah/shisha at 50% (95% CI: 36-64) and lowest for cigarettes at 1% (95% CI: 0.00-0.02) (20). The low rate of flavored cigarette use is likely due to the passage of the 2009 FSPTCA, which banned flavored cigarettes. This study found that young age was associated with flavored tobacco use, as the odds of being a current flavored tobacco user after controlling for menthol use, gender, race/ethnicity and education was 89% higher among 18-24 year olds when compared to 25-34 year olds (20). Estimates from the 2009-2010 National Adult Tobacco Survey found a similar trend; prevalence of flavored cigar use was highest (9.1%, 95% CI: 7.8-10.5) among 18-24 year olds and second highest among 25-44 year olds (3.1%, 95% CI: 2.7-3.6) and decreased with increasing age (28).

In its proposed deeming regulation, the FDA acknowledges the unique role that flavored tobacco products may play in facilitating tobacco use among young populations, noting that "many of the products proposed to be covered by this rule are offered in fruit and candy flavors, such as chocolate and grape flavors, making them especially attractive to children and young adults" (10). Further, in its request for comments on approaches to regulate flavored tobacco, the FDAs specifies that polices should "address the sale of candy and/or fruit-flavored tobacco products to children and young adults" (10).

Dissertation overview and specific aims

The overarching goal of this dissertation is to synthesize existing research related to flavored tobacco use in the U.S., and to translate those findings into evidence that is

useful for FDA decision-makers who are considering policies to regulate the sale of flavored tobacco products.

Specifically, the aims of this dissertation are to:

Aim 1: synthesize existing research examining the use and attitudes/knowledge/perceptions of flavored tobacco use in the U.S., specifically focusing on how age and nonflavored tobacco use are correlated with flavored tobacco use

Aim 2: begin to model the population-level health impact, compared to the status quo, expected to result from a) a ban on combustible flavored tobacco products and b) a ban on all flavored tobacco products, and to organize relevant research that informs the model

Aim 3: determine acceptable ceiling costs for the policies considered in Aim 2, and identify the minimum effectiveness standards at which these interventions would be considered cost-effective and cost-saving

Organization of dissertation

This dissertation is composed of three manuscripts and is organized into six chapters. Chapter 1 (the current chapter) provides background information to contextualize the studies presented in this dissertation, a brief introduction to the dissertation and an overview of the study aims. Chapter 2 describes the conceptual foundation of the

dissertation, provides additional background for Aims 2 and 3, and discusses the study methods used to address Aims 1-3. Chapter 3 addresses Aim 1 through a systematic review of existing literature. Chapter 4 addresses Aim 2 through a decision model that generates expected health effects for the policy options under consideration, and Chapter 5 establishes cost and effectiveness standards for these polices through threshold analyses. The final chapter integrates the study finding from Chapters 3-5 and presents recommendations for future research.

Notes

I employed the first person plural (the editorial "we") throughout this dissertation for readability purposes. However, I conducted most aspects of this research individually. Diana Lock contributed to parts of the systematic review, described in Chapter 3, that required two researchers. My thesis committee contributed in different capacities throughout the planning and execution of this project, primarily by providing guidance on major study design and analytic decisions.

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Chapter 2 – SPECIFIC AIMS AND METHODS

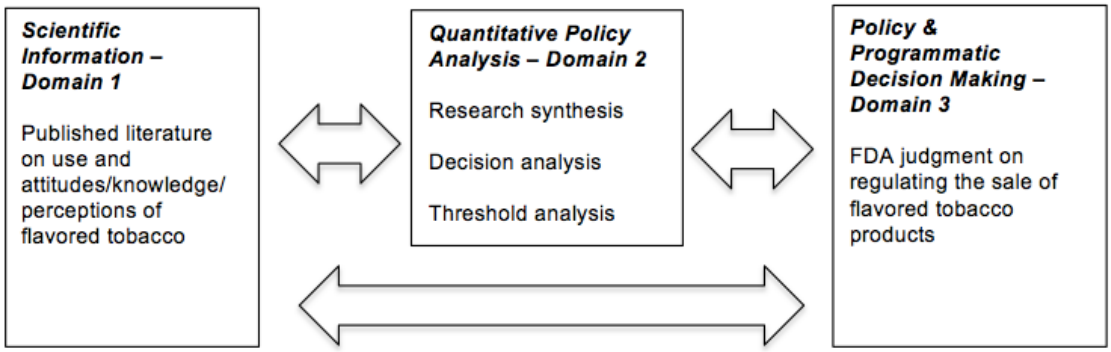
Methodological conceptual framework

The methodological conceptual framework for this project is based upon a "three box model" developed by Holtgrave (1). This model illustrates the ways in which scientific information, quantitative policy analysis, and policy and program decision-making can interact; each domain (that is, each box) simultaneously informs and is informed by the other two. Holtgrave's model is specific to HIV prevention. For this project, we applied the framework to tobacco control.

Figure 2-1 illustrates this dissertation's methodological conceptual framework. The methodologies lie in the "quantitative policy analysis" domain; the primary purpose of these methodologies is to synthesize and translate scientific research into information that is useful and digestible for policy and programmatic decision-makers – that is, to deliver information from the first domain to the third domain. The aims of this dissertation were developed in response to research priorities established by the FDA (the third domain). The results of this project will also serve to set the agenda for future scientific research (the first domain). That is, as research is synthesized and translated, gaps in the scientific literature will be elucidated which, if addressed, would help to improve the results of quantitative policy analyses (which, in turn, would improve the quality of data delivered to policy and program decision-makers).

The methodologies employed for the dissertation, as they relate to aims, are discussed below.

Figure 2-1. Methodological conceptual framework



Aim 1: To synthesize existing research examining the use, attitudes, knowledge and perceptions of flavored tobacco use in the United States, specifically focusing on how age and nonflavored tobacco use are correlated with flavored tobacco use

We used a systematic review to achieve Aim 1. The systematic review is a method used to identify, appraise, synthesize and evaluate research on a specific topic. As opposed to a traditional literature review, a systematic review uses prescribed, transparent methods that are designed to 1) gather all of the available literature on a topic through an extensive search of multiple databases and other resources with relevant literature, 2) extract data and compile estimates of association (if appropriate) between exposures and outcomes of interest, and 3) provide a comprehensive narrative of all of the evidence on a specific topic, including an evaluation of the quality and consistency of the evidence. A systematic review highlights gaps in the literature to inform future research, and can be

used to present synthesized information to decision-makers in an accessible format (2). We describe the details of the methodology for this aim in Chapter 3.

Background for Aims 2 and 3

To assess tobacco control policies in a timeframe that is short enough to inform imminent regulatory decisions, the FDA has shown an interest employing evidence from mathematical modeling studies (3, 4). We employ these types of models to achieve the second and third aims of this dissertation. This section provides a brief overview of some of the ways in which modeling techniques have been employed in tobacco control research to inform policymaking.

Models have been used to inform and evaluate tobacco policy decisions in a variety of ways. Some key uses of models in tobacco control policy have been to: 1) evaluate public health objectives and provide recommendations for developing realistic goals for the future, 2) estimate the financial implications of proposed policies and programs to give decision-makers a sense of the affordability and cost-effectiveness of interventions in comparison to one another, 3) better understand the relationships between factors that influence smoking behaviors by visually and mathematically modeling those relationships, and 4) simulate the impact of policy changes on tobacco behaviors and health outcomes.

In 1990, the U.S. Public Health Service established an objective to reduce the adult smoking prevalence to 13% by 2010. Mendez et al. subsequently developed a dynamic

model in order to determine whether this goal was realistic (5). By using estimates of the changes in overall population size and data from the National Health Interview Survey (NHIS) to model the inflow and outflow of smokers over time—and by testing their model under various assumptions about tobacco use behavior—the authors concluded that the health objective would be very difficult to achieve. The authors noted that failing to meet the objective had the potential to make significant public health successes appear to be unimpressive. While the purpose of modeling is not always to predict the future but, rather, to serve as a heuristic decision tool, Mendez et al.'s model was later shown to have been accurate in its findings (6). In this case, modeling could have been used in advance of setting the Healthy People 2010 goal to help establish objectives that were more feasible.

In another application of modeling, Warner et al. used a simulation model to estimate the net cost and cost-effectiveness of a managed care organization (MCO) covering smoking cessation (7). The authors employed data from multiple MCOs to inform their analysis, and conducted sensitivity analyses in order to explore the role that uncertainty in their data had on the outcome of their of their model. The authors found that, while offering coverage for smoking cessation would modestly increase spending for MCOs, it was a cost-effective intervention that would likely ultimately save money. By conducting this type of analysis, Warner et al. were able to provide decision-makers in MCOs with evidence of the health and cost benefits of implementing a policy that they otherwise may have not considered. While the cost-effectiveness of a policy is often not decision-makers' only consideration when implementing a change, it is often an important one.

The Center for Tobacco Products (CTP) at the FDA – which oversees the implementation of the FSPTCA – has made it a priority to understand the impact of its policies on long-term tobacco use prevalence, morbidity and mortality (8). To meet this goal, the CTP contracted with Sandia National Laboratories to develop a dynamic modeling framework to assess the health-related outcomes in which the Center is interested (8). This framework models the relationships between tobacco use behaviors, policies, marketing educational messages, and other factors thought to influence the outcomes of interest. This model visually represents these relationships, and applies math to quantify them. This type of model bridges theory and data, highlighting what is known and what needs to be better understood in order to gain a comprehensive picture of tobacco use behaviors. Additionally, the Tobacco Products Scientific Advisory Committee, which advises the CTP, held a meeting in April 2014 in which it aimed to learn how modeling techniques can inform CTP decision-making (9). These activities illustrate the FDA's interest in using modeling to better understand the impact of its policies on tobacco-related behavior and health. We developed this dissertation with FDA's methodological interests in mind.

The second and third manuscripts should be viewed as methodologically building upon existing analytic tools and systems science strategies to improve health planning and policies. The SimSmoke model—a simulation model developed by Levy (10)—is an example of the type of model this dissertation builds upon. The SimSmoke model has been used to evaluate tobacco control policies in various contexts by simulating the impact of policy changes on tobacco use and health outcomes. In one application, the

model was used to examine the effects of a ban on menthol cigarettes in the U.S. (11). Levy et al. developed this study to respond to the FDA's need to consider the effect that its policies are likely have on tobacco use initiation, cessation, and overall harm to the U.S. population, and the study's results were used to inform TPSAC's recommendation on menthol cigarettes (4).

This background information provides context for Aims 2 and 3, described below.

Aim 2: To begin to model the population-level health impact, compared to the status quo, expected to result from a) a ban on combustible flavored tobacco products and b) a ban on all flavored tobacco products, and to organize relevant research that informs the model

Decision analyses are used to aid in the making of complex decisions that have important consequences, when a clear preference does not exist (12). Decision analyses are particularly useful tools in the short-term, when a decision needs to be made relatively quickly, and adequate time or resources are not available to conduct new experiments to inform the decision. That is to say, instead of conducting primary research to answer a question, decision analyses employ the best available evidence—or informed guesses, when there is a lack of data—to simulate the potential outcomes of various decision options. While decision analytic models can be predictive if robust data is available to inform them, this is not necessarily their primary purpose. Such models can also be used to synthesize existing knowledge to show decision-makers the consequences expected to

result from different decision alternatives, given what is already known. The decision model used to achieve Aim 2 is a heuristic, rather than predictive model.

A decision tree is a type of decision analytic model; it is a tool that graphically represents the probability that various outcomes will arise as a result of possible decision options (12). To achieve Aim 2, the second manuscript employs a decision tree to compare the consequences of multiple tobacco control policy options and to organize the relevant research that informs the model. We describe the details of the methodology in Chapter 4.

Aim 3: To determine acceptable ceiling costs for the policies considered in Aim 2, and to identify the minimum effectiveness standards at which these interventions would be considered cost-effective and cost-saving

Given that the government has limited resources, decision-makers must consider how the costs of proposed policies compare to one another, whether proposed policies are affordable, and whether they are cost-effective or cost-saving. Threshold analysis is an economic evaluation method that can be used to assess these considerations. Threshold analyses can be used to set performance standards for policies; they can tell you how many infections or cases of disease must be prevented in order for a policy to be considered cost-effective or cost-saving. In order to achieve Aim 3, we conducted threshold analyses to determine acceptable ceiling costs for these policies and to identify the minimum effectiveness standards at which these interventions would be considered cost-effective and cost-saving. Sensitivity analyses provided insight into how uncertainty

in parameter values might impact the interpretation of the results. We describe the details of this methodology in Chapter 5.

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Chapter 3 - Use, Attitudes, Knowledge and Perceptions of Flavored Tobacco Products in the United States: A Systematic Review

ABSTRACT

Introduction: In April 2014, the U.S. Food and Drug Administration released a proposed deeming regulation in which it requested information and data to support the establishment of a product standard that would prohibit characterizing flavors in non-cigarettes tobacco products. The objective of this systematic review is to identify, critically appraise, and summarize research on the use and attitudes/knowledge/perceptions of flavored tobacco products.

Methods: We searched five electronic databases on September 19, 2013 for eligible studies and obtained additional records via grey literature searches, expert contacts and hand searching citations of relevant and included articles. Two independent coders assessed each retrieved record, extracted data from eligible studies and conducted quality assessments. We conducted a qualitative synthesis for included studies.

Results: We included thirty-two studies in this review. The studies exhibited substantial heterogeneity and were of varied methodological quality. The results of these studies highlight the association between flavored tobacco use and young age. Qualitative data collected from adolescents and young adults suggest that flavoring in tobacco products is attractive to these populations. Current evidence addressing how flavored tobacco use might encourage tobacco initiation is inconclusive. Flavored tobacco use may be associated with dual use of other products.

Conclusion: The results suggest that the field would benefit from additional research investigating the use and attitudes/knowledge/perception of flavored tobacco. Valid and reliable measures to investigate these concepts should be standardized to facilitate meta-analyses of multiple studies, and longitudinal data should be collected to track patterns of use over time.

INTRODCUTION

The Family Smoking Prevention and Tobacco Control Act (FSPTCA) of 2009 gave the U.S. Food and Drug Administration (FDA) the ability to regulate tobacco products for the first time. As part of the FSPTCA, cigarettes with characterizing flavors such as cherry, vanilla and grape were banned (1). Notably, this ban did not apply to non-cigarette products. On April 24, 2014, the FDA released a proposed deeming regulation in which it requested information and data to support the establishment of a product standard that would prohibit characterizing flavors in non-cigarette tobacco products (2).

In the deeming regulation, the FDA highlights the relationship between flavored tobacco use and young age, stating that "many of the products proposed to be covered by this rule are offered in fruit and candy flavors, such as chocolate and grape flavors, making them especially attractive to children and young adults…findings indicate that flavored product use may influence tobacco-use patterns in young adulthood, a critical period when lifelong patterns of tobacco use are often established" (2). The FDA specifically asks what actions should be taken "to address the sale of candy and/or fruit-flavored tobacco products to children and young adults," and it requests research to determine the

"likelihood that individuals who engage in flavored tobacco product use will initiate cigarette use and/or become dual users with cigarettes" (2).

The objective of this systematic review is to identify, critically appraise, and summarize research on the use and attitudes/knowledge/perceptions of tobacco products with characterizing flavors in order to inform FDA decision-making. To our knowledge, no such review currently exists. In line with FDA interests, this review focuses specifically on how age and tobacco use status are correlated with flavored tobacco use.

METHODS

Criteria for Considering Studies for this Review

The criteria for studies included in this review were selected in consultation with a team of tobacco control experts.

Types of Studies

We included experimental studies, quasi-experimental studies, observational studies (including case control, cohort and cross sectional studies), case reports, case series, qualitative studies and mixed methods studies in this review.

In terms of types of publication, we included full-length articles, short communications and dissertations reporting results from research studies in this review. We excluded commentaries, news articles, letters, opinion pieces, and review articles.

Types of Participants

We included studies in humans of any age, race/ethnicity, or gender. For a study to be eligible, study participants must have been assessed for at least one exposure of interest, as described below. We excluded studies examining humans at the genetic, cellular or biological level.

Studies conducted with participants outside of the United States were initially included in the search. However, for this report, we focused on studies that recruited participants from the United States. As the purpose of this review is to inform policy decision-making in the United States, we made this decision in order to prioritize studies that are most relevant to this goal. The types of flavored tobacco products sold vary from country to country (3), as does the prevalence of tobacco use (4, 5), chemical makeup of seemingly similar tobacco products (6), and cultural contexts in which tobacco is used (7). Additionally, the regulatory environment with regard to flavored tobacco products has been rapidly changing from country to country in past five years; the product and flavor bans adopted across countries differ from one another, and these regulatory changes have been implemented according to varying timelines (1, 8, 9). Thus, this analysis focused on studies that recruited participants from the United States. A list of international studies that were excluded can be found in **Appendix 3-1**.

Type of Exposure/Intervention

We included studies that examined any type of tobacco product with a characterizing flavor. Given the 2009 FSPTCA's exclusion of menthol in its definition of "characterizing flavor," in the context of this study, any reference to flavored tobacco products should be understood to exclude menthol. We excluded studies that examined the use of flavored products without tobacco (such as products used for nicotine replacement therapy). Electronic cigarettes were included for this review.

Primary exposures and interventions of interest for this review were the use of a tobacco product with a characterizing flavor, or the attitudes/knowledge/perceptions of such products. Attitudes/knowledge/perceptions were defined broadly; these concepts included any rating of the products of interest, indication of having positive or negative perception of these products, and beliefs about these products.

Type of Outcomes

Because the research question for this review does not investigate a specific association but, rather, is intended to be a descriptive synthesis, we focused on outcomes at the "above skin" level; studies examining cellular, genetic and biological-level outcomes were excluded.

Search Methods for Identification of Studies

We searched PubMed, CINHAL, Embase, LILACS and PsychInfo using search strategies designed specifically for each database with input from tobacco control experts and an

experienced informationist from the William H. Welch Medical Library, Johns Hopkins University. Search terms encompassed two concepts: 1) flavors and 2) tobacco products. Flavored terms included multiple derivatives of the word "flavor" (inclusive of American and British spelling conventions), as well as related terms such as "candy," "herb," "spice," "sweet" and "taste." Tobacco terms included a list of tobacco and nicotine products, as well as related words, such as: "smoking," "e-cigarettes," "snus," "waterpipe," "narghila," "bidi," and "smokeless." The complete search strategies are available in **Appendix 3-2**. We searched each database from its inception to September 19, 2013 without any language restriction.

We searched the Global Health Observatory website (http://www.who.int/gho/en/) for grey literature resources on April 19, 2014. We also searched conference abstracts from the World Conference on Tobacco or Health, the Society for Research on Nicotine and Tobacco, and the Society for Research on Nicotine and Tobacco Europe using a list of key terms related to flavors, adapted from the electronic database search terms. We searched all available abstracts online for all years. We attempted to locate full text reports for all abstracts that contained flavor-related key terms. For full texts that could not be located, we contacted authors for additional information about their studies.

We contacted twenty-three domestic and international experts who have conducted work related to flavored tobacco products to identify additional resources. We also hand-searched references from relevant and included studies to identify additional eligible studies.

Study Selection

Working independently, two researchers (SF and DL) reviewed 1) the titles and abstracts, and then 2) the full text articles. At the title and abstract review stage, studies were not excluded based on study design or publication type because we intended to be sensitive in order to capture all relevant literature at this stage. We conducted the full text review in two stages, whereby we first assessed studies based on participants, publication type and study design, and then on exposure of interest. This two-stage review process was used because we narrowed the criteria for eligible exposures after the title and abstract review. While flavored nicotine products and products intended to resemble tobacco or nicotine products (such as candy cigarettes) were initially included in the title and abstract review, they were excluded at the full text review stage in order to focus the review more specifically on products that the FDA might regulate with regard to their flavored content.

We piloted the eligibility criteria on 25 studies prior to proceeding with the review of titles and abstracts, and on 10 studies prior to proceeding with the review of full texts. During each phase of the study selection process, we tagged each study as falling into one of the following categories: 1) both reviewers recommend record for inclusion, 2) both reviewers recommend record for exclusion, or 3) one reviewer recommends record for inclusion and one reviewer recommends record for exclusion. Records in the first and second category were included and excluded, respectively. SF and DL discussed records in the third category to achieve consensus.

Data Extraction

We developed a data extraction form, which was pilot tested by two researchers (SF and DL). The two researchers independently extracted data from each report, including: descriptive characteristics of study participants, study design and methods, prevalence of flavored tobacco use among the entire sample and subgroups, main results related to the use and attitudes/knowledge/perception of flavored tobacco products, funding and ethics, and questions to assess the risk of bias for each study. We implemented data extraction using a Google Form and an accompanying Excel spreadsheet. The data extractors piloted the form until an acceptable level of reliability was achieved. The data extraction items included in the Google Form can be found in **Appendix 3-3**.

Risk of Bias

For each included report, we assessed the risk of selection bias, information bias, bias in the analysis, and reporting bias. For observational studies, we adapted the risk of bias assessment questions from an item bank developed by the Agency for Healthcare Research and Quality for studies of this type (10). For experimental studies, we adapted items from the Cochrane Collaboration's risk of bias assessment tool (11). For qualitative studies, we adapted items from a previous form used in a systematic review of qualitative studies (12). We also consulted other sources for guidance in the development of these questions to ensure that the risk of bias form would be appliable to a diverse set of study designs (13-18). We did not conduct risk of bias assessments for case report/case series studies; we deemed the questions used to assess risk of bias to be not applicable to such reports, given their unique aim and design.

Analysis

We reported descriptive statistics for all studies, including a description of the sample (sample size, age range, mean age (SD), percent male), study aim, flavored tobacco products examined, socioeconomic information, racial and ethnic makeup, nonflavored tobacco use and flavored tobacco use. With regard to data extracted on the use and attitudes/knowledge/perceptions of flavored tobacco, this review focuses on the relationship between flavored tobacco and two study population characteristics: 1) age and 2) tobacco use status. We decided to prioritize these two characteristics, as opposed to other important factors such as race/ethnicity and gender, because internal tobacco industry documents and analyses of the industry's marketing practices have shown that flavored tobacco products are targeted towards young populations (19-21) and, as researchers have noted, are likely intended to entice nonsmoking youth to initiate tobacco use or to encourage novice smokers to continue smoking (19-22). Indeed, in its recent request for flavor-related research, the FDA expressed interest in obtaining information on whether flavored tobacco product use impacts tobacco initiation and/or dual use (2). While industry documents have also shown that flavored products are intended to entice women (21) and minority populations (23) to smoke, FDA interests have largely focused on age and tobacco use status with regard to flavored tobacco. Thus, we focused our data extraction on usage trends and attitudes/knowledge/perceptions by age and tobacco use status.

We performed a qualitative synthesis for all included studies. In terms of reporting study findings, we synthesized results from cohort, quasi-experimental and experimental studies. For these studies, we reported results relating to 1) use of flavored tobacco products and 2) attitudes/knowledge/perception of these products separately. We synthesized results for qualitative and case control/case series studies independently from other studies.

We analyzed results on the attitudes/knowledge/perception of flavored tobacco products by employing a framework proposed by Rees et al. (24). This framework – informed by the Theory of Reasoned Action – proposes that consumer responses to tobacco products can be divided into two broad categories: *perception of the product* and *response to the product*. A feedback loop exists between the two categories and, together, they determine the likelihood of initial tobacco use, experimentation and regular use. A visual of this model proposed by Rees et al. can be found in **Appendix 3-4**. In this model, *perception of the product* is comprised of five domains: risk perception, attitudes and beliefs about the product, social acceptability, outcome expectancies (such as satisfactory nicotine and sensory effects) and future use intentions. *Response to the product* is also comprised of five domains: nicotine reward, taste/sensory effects, conditional cue reactivity, affective and behavioral response, and personal acceptability of the product.

RESULTS

Description of studies

We included thirty-two studies in this review. Of the 23 domestic and international experts we contacted for suggestions for resources, 10 responded. For records with incomplete information for assessment, we were able to locate contact information for authors of 31 of the studies; 16 of the authors responded to inquiries for additional information. The information for 50 records remained incomplete for assessment, as we were unable to obtain the full text or, in cases where no full text exists, detailed information about the study design, execution and results for these studies. Eleven of the records with incomplete information for assessment appear to have been conducted with participants drawn from outside of the United States and, thus, are likely not eligible for this analysis. Of the studies included in this review, almost half (15/32) were published in 2009—the year in which the FSPTCA was passed—or later. **Figure 3-1** illustrates the study selection process, including reasons for exclusion.

Descriptive characteristics of the samples and their prevalence rates for nonflavored tobacco use can be found in **Table 3-1**. Data on flavored tobacco use prevalence is presented in **Table 3-2**, along with other results. Included studies consist of three case studies/case series, fourteen cohort studies, eight experimental or quasi-experimental studies and six qualitative studies. One additional study was included that compiled data from five previously conducted studies, but is not a formal meta-analysis (25). Products examined included kreteks (eight studies), hookah (eight studies), cigars (eight studies),

cigarettes (five studies), smokeless tobacco (five studies), e-cigarettes (four studies), and bidis (two studies).

Cohort, Experimental and Quasi-Experimental Studies

Use of flavored tobacco products

Table 3-2 provides data on the use of flavored tobacco products. This table is comprised of three sections:

1) Flavored tobacco use assessed by age. This section includes cross-sectional data on flavored tobacco use by age, as well as for the entire sample (if reported), and results from statistical tests that assess the relationship between age and flavored tobacco use.

2) Flavored tobacco use assessed by tobacco use status. This section includes cross-sectional data on dual use, patterns of flavored tobacco use over time, and results of statistical tests that assessed the relationship between flavored tobacco use and tobacco use behavior in general.

3) Prevalence data on flavored tobacco use for all included studies that provide such data, but did not report these data by age or tobacco use status. If reported, prevalence for the entire sample is recorded in this section of **Table 3-2**. Three studies did not report prevalence for the entire sample (26-28); prevalence for these studies is reported according to school grade.

Results from this table are described below.

Flavored tobacco use and age

Research suggests that flavored tobacco use is associated with young age. This relationship was assessed in six studies (25, 26, 29-33). The results of these studies can be found in the first section of **Table 3-2**. In the three studies that examined national samples, flavored tobacco use consistently increased with younger age (29, 31-33). Two studies statistically assessed the relationship between flavored tobacco use and age by examining age as a dichotomous variable (29, 30). Villanti et al. found that younger age (18-24) was significantly associated with flavored tobacco use when compared with older age (25-34), while Vander Weg et al. (2008) found no relationship between younger age (<20 years old) and flavored tobacco use when compared with older age (≥20 years old). These varying results can, perhaps be attributed to the different samples. The study by Villanti et al. was conducted with a nationally representative sample, while the study by Vander Weg et al. (2008) examined use among military recruits, who may be more inclined towards tobacco use in general when compared with the general population (34, 35).

Two studies examined other measures related to flavored tobacco use and age. Oliver et al. combined data from five previously conducted treatment or switching studies (36-40) and found no significant differences between current flavored and nonflavored smokeless tobacco users with regard to their mean age of first dip or mean age of daily/regular use. Soldz et al. (2003) found that the mean age of initiation for current kretek users was significantly higher than that for cigarettes and cigars, and there was no significant difference in mean age of initiation when compared to bidis (26). These findings do not

directly speak to the role that flavoring plays in tobacco use initiation, as these data do not indicate whether the product used at initiation was flavored.

Flavored tobacco use and tobacco use status

Five studies assessed the relationship between flavored tobacco use and tobacco use patterns, including dual use and progression to other tobacco products (25, 26, 29, 30, 41). Cigarette smoking (30) and smokeless tobacco use (41) were associated with a significant increase in kretek use (OR=10.53, 99% CI: 8.41-13.20, p<.001 and OR=1.23, 95% CI: 1.01-1.49, p=.04, respectively) and use of any menthol product was associated with a significant increase in any current non-menthol flavored tobacco use (OR=2.28, 95% CI: 1.42-3.67, p<0.001) (29). Data from current smokeless tobacco users examining their flavored/nonflavored brand choices over time – from initiation to regular use to current use – suggested that flavoring may play a role in the maintenance of smokeless tobacco use (25). In a study conducted by Oliver et al., more current smokeless tobacco users chose a flavored product over a nonflavored product for first time use, first regular use and first daily use (25). Conversely, one study examined smoking initiation precedence among smokers of kreteks and other combustible tobacco products (cigars, bidis, and cigarettes – flavoring not specified, but assumed to be nonflavored) and found that, in all cases, the percent of individuals who initiated with kreteks was lower than the percent who initiated with the comparator product (26). Thus, evidence suggests that there may be an association between flavored tobacco use and dual use, and there is mixed evidence showing that flavored tobacco use facilitates progression to other tobacco products.

Flavored tobacco use – prevalence

Table 3-2 also provides data on flavored tobacco use prevalence that was not assessed by age or tobacco use status. Six of these studies examined use of kreteks (26-28, 30, 42, 43); three examined cigarettes (29, 44, 45) and hookah (29, 42, 46); two examined smokeless tobacco (25, 29) and cigars (29, 44); and one examined bidis (28), pipes (29), and e-cigarettes (29). Of the 28 measures included in this section of the table, only one gives information about the frequency of use of a flavored product (45); all other measures provide information on current, ever or never use.

Attitudes/Knowledge/Perception

Thirteen studies examined the attitudes/knowledge/perception of flavored tobacco products (27, 43, 45, 47-56). Of these studies, seven provided data on preferred flavored of tobacco (47, 49, 51-54, 56). The results of these measures can be found in **Table 3-3**. Fruit and mint flavors were popular, mentioned in six of these studies (47, 49, 51, 52, 54, 56). Dawkins et al. assessed e-cigarette flavor choice by smoking status and found that current and ex-smokers did not differ with respect to their flavor preferences (51).

Beyond flavor preference, seven studies assessed other measures of attitudes/knowledge/perception (27, 43, 45, 48-50, 55). These were analyzed by employing a framework proposed by Rees et al., described in the Methods section (24). We found four studies that assessed the domains encompassed by *perception of the*

product (27, 45, 48, 55). Two of these studies assessed attitudes and beliefs about the product (27, 45), four studies examined use intentions (27, 45, 48, 55), two studies examined outcome expectancies (27, 55), one study examined risk perception (27), and no studies examined social acceptability of these products. These results can be found in **Table 3-4**.

The studies examining *perception of the product* differ in study design and analytic approaches. Manning et al. and Ashare et al. asked participants to rate flavored and nonflavored cigarette packages and advertisements, respectively (45, 55). Manning et al. examined sensation seeking (the preference for high stimulus arousals) as a mediator between package exposure and outcomes (hedonic beliefs, brand attitude and trial intentions), while Ashare et al. examined smoking status as a mediator between advertisement exposure and outcomes (positive and negative expectancies, and willingness to try). Soldz et al. (2005) asked participants to endorse statements about kreteks, some of which made comparisons to cigarettes; the authors examined results according to smoking status. Lastly, Pepper et al. assessed trial intentions among all respondents for flavored e-cigarettes versus e-cigarettes that had no flavor descriptor. The different study designs and analytic approaches preclude making a definitive overarching statement about whether "flavor matters" with regard to perception of tobacco products. However, a qualitative assessment of the results in **Table 3-4** suggests that flavoring may impact the perception of tobacco products, giving respondents a more favorable perception of these products, and that smoking status may act as a mediator; positive perceptions of flavored tobacco products may increase with smoking intensity. This

assessment is made, however, without in-depth knowledge of the domains that were less-assessed – i.e. social acceptability and risk perception.

We found three studies that assessed the domains encompassed by *response to the product* (43, 49, 50). Two of these studies (43, 50) used items drawn from the Duke Sensory Questionnaire (DSQ) (57) and the Cigarette Evaluation Scale (CES) (58, 59). The third study used items from the DSQ, as well as measures from another study to assess "harshness," "irritation" and "strength" (62) (54). All items were anchored on seven-point Likert scales (1='not at all,' 7='extremely' or 'very'). Some items were collapsed to make composite scores, noted in **Table 3-5**. The way in which the item-specific results were presented suggests that there may have been some variation across the three studies with regard to the way these measures were implemented. For example, Malson et al. (2002) and Malson et al. (2003) differ in the way certain items are described ("similarity to own brand" versus "different from their own brand"). Results in **Table 3-5** reflect the wording that was used to report measures in each paper. Reflective of reporting, only significant results are presented for Malson et al. (2003). The authors of this study state that "[a]ll other differences in subjective items were not statistically significant"(43). While the authors report using DSQ and CES items, they do not explicitly confirm that all items were assessed; thus, data on non-significant results for Malson et al. (2003) are missing from **Table 3-5**.

The role that flavor plays in consumer product response is unclear; results are mixed with regard to how flavored products were rated when compared to nonflavored products. For

example, all three studies examined items assessing liking of the products. Malson et al. (2002) found that the strawberry Irie bidi was rated lower than participants' own brand (a conventional cigarette) for liking (4.8 ± 0.9 versus 6.3 ± 0.7, respectively), but higher than the unflavored Sher bidi (3.9 ± 1.6) and the American Spirit cigarette (3.1 ± 2.2); Malson et al (2003) found that participants rated a clove cigarette higher than their own brand (a conventional cigarette) (6.1±0.5 versus 4.8±0.4, respectively); and O'Connor et al. found that participants rated a flavored cigarette (Camel Exotic) lower than an unflavored light cigarette (Camel Light) (3.0 (0.2) versus 4.5 (0.2), respectively). The lack of a discernable pattern in these results suggests that, 1) in measuring consumer responses to flavored tobacco products, the comparator products chosen from the wide range of unflavored tobacco may impact the direction and magnitude of the results, and 2) consumer responses to flavored tobacco products may differ by specific product or flavor (i.e. all flavored tobacco products do not elicit equal responses).

Risk of Bias – Cohort, Experimental and Quasi-experimental studies

Results from the risk of bias assessment for the 23 studies described above can be found in **Table 3-6**. Six studies were vulnerable to selection bias, as they either provided concerning or incomplete descriptions of their recruitment strategies (26, 27, 32, 47, 49, 55), one of which may have also applied varying inclusion/exclusion criteria across participants (47). The study conducted by Oliver et al (25), though not designed as a formal meta-analysis, combined data from five previous studies (36-40) and may have also been subject to selection bias; the way in which the previously conducted studies were identified was not clearly described. All studies may have been subject to

information bias, as the reliability and validity of all measures used were not established in any of the papers examined. Six studies may have been subject to information bias for not applying measures consistently across all study participants (45-47, 49, 51, 56).

Qualitative Studies

The six qualitative studies differed with regard to their study purposes. Some studies explored questions that yielded in-depth findings with regard to flavored tobacco products, while others touched on relevant results, but were primarily focused on other themes. Thus, some studies produced richer flavor-related data than others.

All of the qualitative studies examined adolescent or young adult populations. Two studies (60, 61) also included participants older than the age of 26. The qualitative studies were geographically diverse; settings included New York, Minnesota, Pennsylvania, Texas, Tennessee and Ohio. Data collection methods varied across studies. Three studies employed focus groups (42, 61, 62), two employed interviews (63, 64), and one employed observations and interviews (60). These studies examined diverse tobacco products, including non-combustible tobacco products (61-63), cigars (60), hookah (64), and hookah and cloves (42).

Findings from the qualitative studies can be found in **Table 3-7**. Participants in all six studies perceived characterizing flavors in tobacco products to be an attractive attribute. Flavoring was seen as an appealing trait (61-63) and disguised risks of tobacco consumption (64). Participants in one study noted that flavoring of cigar products served

a functional use, as the flavoring concealed the smell of marijuana when cigars were used for blunts (60). Kreteks were also viewed positively for a functional purpose; participants noted that these products lasted longer than conventional cigarettes (42). Only one study (42) noted an undesirable attribute of a flavored product - that kreteks can be hard to locate for purchase and thus can be inconvenient to use. Together, the qualitative studies provide evidence that characterizing flavors in tobacco products are viewed as an attractive trait among users and nonusers of these products.

Risk of Bias – Qualitative Studies

The risk of bias assessment can be found in **Table 3-8**. All of the studies were likely or potentially subject to recruitment bias, as recruitment strategies may have differed from participant to participant. Saturation was not mentioned in any of the six studies, and only one study confirmed that it performed member checking (63), potentially calling into question the validity of the findings. In considering the design of the included qualitative studies and their assessed risk of bias, the reviewers indicated that the conclusions drawn in half of the studies were questionable and not strongly supported (42, 60, 61).

Case Studies/Case Series

Three case studies/case series met the inclusion criteria for this review (65-67). Two studies examined illness following kretek use (65, 66), and one study examined illness following cigar use (67). These studies elucidate potential questions for future research around acute illnesses that may result from the use of flavored tobacco products.

DISCUSSION

The 32 studies included in this review represent the literature conducted on the use and attitudes/knowledge/perception of flavored tobacco products in the United States. The high number of studies (50) that had incomplete information for assessment likely reflects the recent interest in flavored tobacco; many of these studies are abstracts that were presented at recent conferences. The included studies exhibited substantial heterogeneity with regard to products and populations examined, as well as the study designs and measures employed. The studies were of varied methodological quality.

The results of these studies highlight the association between flavored tobacco use and young age. In national samples, flavored tobacco use consistently increased with decreasing age, and qualitative data collected from adolescents and young adults suggest that the flavoring in tobacco products is attractive to these populations. Current evidence addressing how flavored tobacco use might encourage tobacco initiation is inconclusive; however, evidence suggests that flavored tobacco use may be associated with dual use. There are no "gold standard" studies that address these questions.

The risk of bias assessment points to the need for more rigorously conducted qualitative studies to assess the use, attitudes, knowledge and perceptions of tobacco products with characterizing flavors. All studies may have been subject to information bias, as the reliability and validity of all measures used were not established in any of the papers examined. This may be because many measures in the field of tobacco control research have been used for a long time and may be thought to be well-established (68). However,

research shows that self-reported measures may be particularly problematic when used in adolescent populations (69), a target audience for flavored tobacco products.

Additional research is needed to investigate how flavored tobacco use impacts tobacco use initiation and patterns of use in generalizable populations. To expand the evidence on the use of flavored tobacco products, future studies should ideally collect longitudinal data in a generalizable population. Following a group of naïve smokers over time to examine how flavoring impacts tobacco use initiation, progression to other tobacco products and dual use would be ideal. However, the FDA appears to be interested in ruling on flavored tobacco products in the near future, and waiting for the results of a longitudinal study may not be practical. To assess potential flavored-related policies in timeframe that is short enough to inform imminent regulatory decisions, then, the FDA might consider synthesizing existing evidence to inform decision models examining the results of various policy options. Such a model should consider how ruling on specific flavored products might impact initiation and switching patterns between tobacco products, as well as the ways in which the detrimental health effects of tobacco use vary according to product and duration of use.

With regard to the relevancy of these results to FDA decision-making, it is noteworthy that none of the studies included in this review assessed the ways in which the use or attitudes/knowledge/perceptions of flavored tobacco has changed as a result of flavored tobacco product bans. Pre-post studies that survey individuals before and after the

implementation of a flavored tobacco product ban could generate knowledge to directly inform to FDA regulatory decisions.

This review is subject to several limitations. In scope, this review was restricted to participants recruited in the United States, and it focused on age and tobacco use as correlates of the use and attitudes/knowledge/perception of flavored tobacco products. In focusing the analysis in this way, results from studies conducted in other countries remain unknown, and important findings such as those elucidating relationships between socioeconomic status or race/ethnicity and tobacco use are potentially overlooked. However, this review is intended to inform FDA decision-making and, thus, the results of this study highlight the most relevant data available at this time. As noted in the Results, interest in flavored tobacco use has piqued in recent years. It is likely that new research has been conducted and disseminated since the time at which studies were collected for this review, and this study does not reflect the findings of those studies. Thus, the topics investigated in this review should continue to be explored as new research is conducted. A primary strength of this study includes the thorough search for eligible records – a process which included searching multiple electronic databases, conferences abstracts and grey literature resources, contacting experts, and hand searching all included studies. The broad inclusion criteria used to identify studies looking at the attitudes/knowledge/perception of flavored products is also a strength of this study. By broadly defining these concepts, we were able to capture the range of studies that have examined attitudes/knowledge/perception in different ways.

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Appendix 3-1. International studies that were not included in the analysis

Study ID is defined as: First author, year of publication

- **Study ID (Citation):** Akhter, 2008 (70)
  Country: Bangladesh
  Title: Relationship between betel quid additives and established periodontitis among Bangladeshi subjects
- **Study ID (Citation):** Amin, 2010 (71)
  Country: Saudi Arabia
  Title: Harm perception, attitudes and predictors of waterpipe (shisha) smoking among secondary school adolescents in Al Hassa, Saudi Arabia
- **Study ID (Citation):** Borgan, 2013 (72)
  Country: Bahrain.
  Title: Beliefs and perceptions toward quitting waterpipe smoking among café waterpipe tobacco smokers in Bahrain
- **Study ID (Citation):** Etter, 2010 (73)
  Country: France, Canada, Belgium, Switzerland
  Title: Electronic cigarettes: a survey of users
- **Study ID (Citation):** Figueiredo, 2012 (74)
  Country: Brazil
  Title: Use of flavored cigarettes among Brazilian adolescents: a step toward nicotine addiction?
- **Study ID (Citation):** Gunaseelan, 2007 (75)
  Country: Areca nut use among rural residents of Sriperambudur Taluk: a qualitative study
  Title: India
- **Study ID (Citation):** Hammond, 2013 (76)
  Country: United Kingdom
  Title: The effect of cigarette branding and plain packaging on female youth in the United Kingdom
- **Study ID (Citation):** Israel, 2003 (77)
  Country: Water pipe (sisha) smoking in cafes in Egypt
  Title: Egypt
- **Study ID (Citation):** Leatherdale, 2011 (78)
  Country: Canada
  Title: Cigar, cigarillo, and little cigar use among Canadian youth: are we underestimating the magnitude of this problem?
- **Study ID (Citation):** Nakhostin-Roohi, 2010 (79)
  Country: Iran
  Title: Hookah smoking in students: prevalence, pattern of smoking, situational characteristics and motivation of use
- **Study ID (Citation):** Soetiarto, 1999 (80)
  Country: Indonesia
  Title: The relationship between habitual clove cigarette smoking and a specific pattern of dental decay in male bus drivers in Jakarta, Indonesia
- **Study ID (Citation):** White, 2012 (81)
  Country: Brazil
  Title: The potential impact of plain packaging of cigarette products among Brazilian young women: an experimental study
- **Study ID (Citation):** WHO, 2010 (82)
  Country: Egypt
  Title: Global Adult Tobacco Survey (GATS) Egypt - Country Report 2009

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Appendix 3-2. Electronic database search terms

Database	Flavor key terms	Tobacco key terms
PubMed	Flavoring Agents* [Mesh] OR "flavor"[tw] OR "flavour"[tw] OR "flavors" [tw] OR "flavours"[tw] OR "flavored"[tw] OR "flavoured"[tw] OR "flavoring"[tw] OR "flavouring"[tw] OR "candy" [Mesh] OR "candy"[tw] OR "herb"[tw] OR "spice"[tw] OR "sweet"[tw] OR "taste" [Mesh] OR "taste" [tw] OR "clove" [tw] OR "sweetening agents" [Mesh] OR ("additive"[tw] AND "tobacco"[tw]) OR ("additives"[tw] AND "tobacco"[tw])	"Smoking" [Mesh] OR Tobacco* [Mesh] OR Tobacco, Smokeless* [Mesh] OR "Tobacco Products" [Mesh] OR "Tobacco Use Cessation" [Mesh] OR "tobacco" [tw] OR cigar* [tw] OR "bidi"[tw] OR "bidis"[tw] OR "smokeless"[tw] OR "snus"[tw] OR "smoker"[tw] OR "smokers"[tw] OR "e-cigarette"[tw] OR "e-cigarettes" OR "nicotine" [tw] OR Nicotine*[Mesh] OR "hookah" [tw] OR "waterpipe" [tw] OR "waterpipes" [tw] OR "shisa" [tw] OR "narghile" [tw]
CINAHL	MW Flavoring Agents OR Flavor OR Taste OR TX flavor* OR flavour* OR candy OR herb OR spice OR spices OR sweet OR taste OR clove OR "sweetening agents" OR (TX "additive" AND "tobacco") OR (TX "additives" AND "tobacco")	MJ Smoking OR Tobacco OR Smokeless OR TX Smoking OR Tobacco OR Smokeless OR cigar* OR bidi OR bidis OR snus OR smoker OR smokers OR e-cigarette* OR nicotine OR hookah* OR waterpipe* OR water-pipe* OR shisha OR narghile
LILACS	MH:"Flavoring Agents" OR MH:"sweetening agents" OR MH:"candy" OR MH:"spices" OR MH:"taste" OR flavor$ OR flavour$ OR flavored OR flavoured OR flavoring OR flavouring OR herb OR taste OR clove OR sweet OR doce OR dulce OR additive$ OR aditivo	MH:"tobacco" OR MH:"Smoking" OR MH:"Cigarette" OR MH:"tobacco, smokeless" OR MH:"tobacco use cessation" OR MH:"tobacco products" OR MH:"Smoking Cessation" OR MH: "tobacco use disorder" OR MH: "Consumption of tobacco-derived products" OR tobacco OR bidi$ OR smokeless OR snus OR e-cigarette$ OR cigarette$ OR cigarillo$ OR cigar$ OR charuto OR smoker$ OR fumador OR fumante OR nicotine OR nicotina OR hookah OR narguille OR narghile OR waterpipe$ OR water-pipe$ OR cachimbo$ OR pipa OR shisha
PychInfo	SU Taste Perception OR "Flavoring Agents" OR "flavor" OR "flavour" OR "flavors" OR "flavours" OR "flavored" OR "flavoured" OR "flavoring" OR "flavouring" OR "candy" OR "herb" OR "spice" OR "sweet" OR "taste" OR "clove" OR "sweetening agents" OR ("additive" AND "tobacco") OR ("additives" AND "tobacco"	SU Tobacco Smoking OR SU Smokeless Tobacco OR SU Smoking Cessation OR SU Nicotine OR "Smoking" OR "Tobacco" OR "Smokeless Tobacco" OR "Tobacco Products" OR "Tobacco Use Cessation" OR "tobacco" OR "cigar" OR "cigars" OR "cigarette" OR "cigarettes" OR "cigarillo" OR "cigarillos" OR "bidi" OR "bidis" OR "smokeless" OR "snus" OR "smoker" OR "smokers" OR "e-cigarette" OR "e-cigarettes" OR "nicotine" OR "hookah" OR "waterpipe" OR "waterpipes" OR "shisa" OR "narghile"
Embase	'flavoring agent' OR 'flavor':ab,ti OR 'flavour':ab,ti OR 'flavors':ab,ti OR 'flavours':ab,ti OR 'flavored':ab,ti OR 'flavoured':ab,ti OR 'flavoring':ab,ti OR 'flavouring':ab,ti OR 'candy':ab,ti OR 'sugar' OR 'herb' OR 'herb':ab,ti OR 'spice' OR 'spice':ab,ti 'sweet':ab,ti OR 'sweetness' OR 'taste' OR 'taste':ab,ti OR 'clove' OR 'clove':ab,ti OR 'sweetening agent'/mj OR ('additive':ab,ti AND 'tobacco':ab,ti) OR ('additives':ab,ti AND 'tobacco':ab,ti)	'Smoking' OR 'tobacco'/exp OR 'tobacco':ab,ti OR 'smokeless tobacco' OR 'smoking cessation' OR 'cigar':ab,ti OR 'cigars':ab,ti OR 'cigarette':ab,ti OR 'cigarettes':ab,ti OR 'cigarillo':ab,ti OR 'cigarillos':ab,ti OR 'bidi':ab,ti OR 'bidis':ab,ti OR 'smokeless':ab,ti OR 'snus':ab,ti OR 'e-cigarette':ab,ti OR 'e-cigarettes':ab,ti OR 'nicotine' OR 'nicotine gum' OR 'hookah':ab,ti OR 'waterpipe':ab,ti OR 'waterpipes':ab,ti OR 'shisa':ab,ti OR 'narghile':ab,ti

Appendix 3-3. Data extraction form (conducted with Google Forms)
Note: Some questions in this form were answered in an Excel sheet; this sheet is not shown here.

Flavor Review -- Data Extraction Form
*Required

1. StudyID (First author, year of publication) *
2. Authors *
3. Title *
4. Journal *
5. Year of Publication *
6. Volume *
7. Issue *
8. Page Numbers *
9. Reviewer * *Mark only one oval*
    - Shari
    - Diana

Descriptive Characteristics of Study Participants
Answer all questions for the total sample -- i.e., the participants answering questions about flavored tobacco. (For qualitative studies, if flavors are not specifically asked about but simply emerged as a theme, the total sample is all participants in the study.)

If the paper contains two DISTINCT samples (the participants are both recruited separately and the characteristics for each group are ONLY reported separately), fill out all information for the two groups

Use the following format when there are two groups:

Total study sample
Group1 30; Group2 41

Age: Range
Group1 15--17; Group2 18+

10. Total study sample
Enter "n." If it is not reported or you cannot identify the number, enter "NR/Can't tell."

11. Age: Range
If it is not reported or you cannot identify the number, enter "NR/Can't tell."

12. Age: Mean
If it is not reported or you cannot identify the number, enter "NR/Can't tell."

13. Age: SD
If it is not reported or you cannot identify the number, enter "NR/Can't tell."

14. Age: SE
If it is not reported or you cannot identify the number, enter "NR/Can't tell."

15. Age: CI
Enter the 95% CI using the following format: 20-60. If something other than the 95% CI is reported, please specify (e.g. 90% CI: 30--60). If it is not reported or you cannot identify the number, enter "NR/Can't tell."

16. Sex: Males
Enter: n (%). If it is not reported or you cannot identify the number, enter "NR/Can't tell."

17. Sex: Females
Enter: n (%). If it is not reported or you cannot identify the number, enter "NR/Can't tell."

18. Specify countries in which participants were recruited
Type "NR" for not reported. If more than one country, separate them by semicolon (;). Do NOT put period at the end. For all countries, spell out country name (e.g., United Kingdom rather than UK)

19. If applicable, go to the Excel spreadsheet and fill out information for: Race/Ethnicity, Tobacco Use Status, and SES.*
When complete, write "done" in the box below

20. Notes on this section
Enter questions, areas of confusion, information that you think should be highlighted, shortcomings in the form in capturing relevant information

Study Design and Methods

21. Study aim
Record verbatim, with quotation marks, the study aim described in one of the following sections of the article using this order of priority: Introduction, Abstract, and other sections of this article. Type "NR" if there is no study aim found in this article.

22. Inclusion/Exclusion criteria
Record verbatim, with quotation marks, the inclusion/exclusion criteria for participants described in one of the following sections of the article using this order of priority: Methods, Abstract, and other sections of this article. Type "NR" if there is no inclusion/exclusion criteria found in this article.

23. Study Design
Mark only one oval.

- o Case control
- o Case report
- o Case series
- o Cohort – cross sectional (one time point)
- o Cohort – cross sectional (multiple time points)
- o Cohort – prospective
- o Cohort – retrospective
- o Experimental
- o NR/Can't tell
- o Qualitative
- o Quasi-experimental
- o Mixed methods
- o Nested case control
- o Other: _____

24. Use/attitude/knowledge/perception assessed for the following FLAVORED tobacco products
Check all that apply.

- ▫ Betel quid
- ▫ Bidis
- ▫ Chew
- ▫ Cigar products (cigars, little cigars, cigarillows)
- ▫ Cigarettes
- ▫ E-cigarettes
- ▫ Gutkah
- ▫ Hookah/water pipe
- ▫ Kreteks/cloves
- ▫ Pipes
- ▫ Snus
- ▫ Spit
- ▫ Orbs
- ▫ Other combustible products
- ▫ Other non-combustible products
- ▫ NR/Can't tell

25. Notes on this section

Prevalence of Flavored Tobacco Use

26. Is the prevalence of flavored tobacco use reported in this study, either for the total sample or for specific subgroups (or both)?
Mark only one oval

- Yes
- No → *After the last question in this section, skip to question 29*
- Can't tell, Shari and Diana to discuss → *After the last question in this section, skip to question 29*

27. If "Yes," go to the Excel document and enter prevalence information
When complete, write "done" in the box below

28. Notes for this section
Enter questions, areas of confusion, information that you think should be highlighted, shortcomings in the form in capturing relevant information

Main Results Section
Fill this section out if there is information related to the use/attitudes/knowledge/perceptions of flavored tobacco use (beyond prevalence information) reported in the paper.

29. Please go to the Excel spreadsheet and fill out information for the Results sections
When complete, type "done" in the box below

30. Notes for this section
Enter questions, areas of confusion, information that you think should be highlighted, shortcomings in the form in capturing relevant information

Funding and Ethics

31. Was the source(s) of monetary or material support ("funding") for study reported in article?
Mark only one oval.
- Yes
- No

32. If "Yes" to above, specify funding source
If "No" to above, type "n/a"

33. Did the author report any conflict of interest?
Mark only one oval.
- One or more authors reported a conflict of interest
- All authors reported NO conflict of interest
- NR/Can't tell

34. If applicable, did the authors report an ethical review?
Mark only one oval.
- Yes
- No
- Not applicable

35. Notes on this section
Enter questions, areas of confusion, information that you think should be highlighted, shortcomings in the form in capturing relevant information

Risk of Bias

36. Do the inclusion/exclusion criteria vary across the comparison groups of the study? *
For studies with one group, replace "groups" with "individuals."
Mark only one oval.
- Yes, varies ("flag")
- Partially: some, but not all criteria, applied to all groups or not clearly stated if some criteria are applied to all groups/individuals ("flag)
- No, does not vary (no flag)
- Cannot determine: article does not specify, but seems that application across groups/individuals does not vary (no flag)
- Cannot determine: article does not specify, but seems that application across groups/individuals might vary ("unsure flag")

37. Explanation for rating

If notes for the previous question, please include. If no notes, write "n/a"

38. Does the strategy for recruiting participants into the study differ across groups? *
For studies with one group, replace "groups" with "individuals."
Mark only one oval.
- o Yes, differs ("flag")
- o No, does not differ (no flag)
- o Cannot determine, but seems that strategy may differ ("unsure flag")
- o Cannot determine, but strategy does not seem to differ (no flag)

39. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

40. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?
Please take into consideration the study design.
Mark only one oval.
- o Yes, inappropriate ("flag")
- o No, not inappropriate (no flag)
- o Cannot determine or no description of the derivation of the comparison group ("unsure flag")
- o Not applicable: study does not include a comparison group (case series, one study group)

41. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

42. Does the study fail to account for important variations in the execution of the study from the proposed protocol?
Consider intensity, duration, frequency, route, setting, and timing of intervention/exposures.
Mark only one oval.
- o Yes, fails to account ("flag")
- o Partially, fails to account ("flag")
- o No, does not fail to account (no flag)
- o Cannot determine ("unsure flag")
- o Not applicable: not an intervention study or no variations

43. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

44. Was the outcome assessor not blinded to the intervention or exposure status of participants?
Mark only one oval.
- o Yes, not blinded ("flag")
- o No, blinded (no flag)
- o Not applicable: assessor cannot be blinded
- o Applicable, but can't tell/not discussed ("unsure flag")

45. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

46. Were valid and reliable measures used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participant health benefits and harms, and confounding?
Mark only one oval.
- o Yes, valid and reliable measure used (no flag)
- o No, valid and reliable measure not used ("flag")
- o Cannot determine or measurement approach not reported; the authors did not discuss the reliability and/or validity of the measures used ("unsure flag")

47. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

48. Were the measures used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participant health benefits and harms, and confounding implemented consistently across all study participants?
Mark only one oval.

- o Yes, measures were implemented consistently across all study participants (no flag)
- o Partially; some measures used consistently across all study participants ("flag")
- o No, measures were not used consistently across all study participants ("flag")
- o Cannot determine or measurement approach not reported;; the authors did not discuss whether their measures were implemented consistently, but seems OK (no flag)
- o Cannot determine or measurement approach not reported;; the authors did not discuss whether their measures were implemented consistently, but seems questionable ("unsure flag")

49. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

50. Was the length of follow--up different across study groups?
For studies with one group, replace "groups" with "individuals." If different lengths of follow--up were adjusted by statistical techniques, (e.g., survival analysis), the answer is no. Studies in which differences in follow--up were ignored should be answered yes.
Mark only one oval.

- o Yes, different ("flag")
- o No, not different or remedied through analysis (no flag)
- o Not applicable: cross--sectional
- o Applicable but cannot determine ("unsure flag")

51. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

52. In cases of high loss to follow--up (or differential loss to follow--up), was the impact assessed (e.g., through sensitivity analysis or other adjustment method)?
Attrition is measured in relation to the time between baseline (allocation in some instances) and outcome measurement for both retrospective and prospective studies and could include data loss from switching. Attrition rates may vary by outcome and time of measurement. Apply criterion for relevant standards for the study design and topic. Cochrane standard for attrition is 20 percent for shorter term (<1 year) and 30 percent for longer term (≥ 1 year).
Mark only one oval.

- o Yes, impact assessed (no flag)
- o No, impact not assessed ("flag")
- o Cannot determine ("unsure flag")
- o Not applicable: no loss to follow--up or loss to follow--up was not considered to be high, cross-sectional study, or case--control study selected on outcome

53. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

54. Are any important primary outcomes missing from the results?
Mark only one oval.

- o Yes, important outcome(s) missing ("flag")
- o No important outcome(s) missing (no flag)
- o Cannot determine ("unsure flag")

55. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

56. Are results believable taking study limitations into consideration?
Please consider other sources of bias that have not been asked about (and if they exist, make note in the explanation section). Please also consider biases that have been asked about in other questions in this form, and whether those biases undermine the believability of the results.
Mark only one oval.

- o Yes, believable (no flag)
- o No, not believable ("flag")

- Unsure ("unsure flag")

57. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

58. Any attempt to balance the allocation between the groups or match groups (e.g., through stratification, matching, propensity scores).
Mark only one oval.
- Yes or study accounts for imbalance between groups through a post hoc approach such as multivariate analysis (no flag)
- No or cannot determine ("flag")
- Not applicable: study does not include a comparison group (case series or one study group)

59. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

60. Were important confounding variables not taken into account in the design and/or analysis (e.g., through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?
Please consider tobacco use status as a confounding variable. Please also consider what each study is asking, and other confounding variables that might be appropriate to consider.
Mark only one oval.
- Yes, not accounted for or not identified ("flag")
- Partially: some variables taken into account or adjustment achieved to some extent ("flag")
- No: taken into account (no flag)
- Cannot determine ("unsure flag")
- Not applicable: this study that does not try and establish the causal association between an exposure and outcome

61. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

62. Were the techniques employed in the analysis appropriate for the study design and question of interest?
Mark only one oval.
- Yes (no flag)
- No ("flag")
- Cannot determine;; not clearly stated;; not sure ("unsure flag")

63. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

64. Where applicable, was the allocation sequence adequately generated?
Mark only one oval.
- Yes (no flag)
- No ("flag")
- Applicable, but can't tell ("unsure flag")
- Not applicable for this study

65. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

66. Where applicable, was the allocation adequately concealed?
Mark only one oval.
- Yes (no flag)
- No ("flag")
- Applicable, but can't tell ("unsure flag")
- Not applicable for this study

67. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

68. Where applicable, was knowledge of the allocated intervention adequately prevented during the study?

Mark only one oval.

- o Yes (no flag)
- o No ("flag")
- o Applicable, but can't tell ("unsure flag")
- o Not applicable for this study

69. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

70. Is this a qualitative study?
Mark only one oval.

- o Yes
- o No → *Stop filling out this form.*

Risk of Bias – Qualitative Study Questions

71. Were the data transcribed verbatim (i.e., were audiotapes, videotapes, or field notes used)?
Mark only one oval.

- o Yes, data transcribed verbatim (no flag)
- o No, data not transcribed verbatim ("flag")
- o Can't tell/not discussed ("unsure flag")

72. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

73. For interviews and focus groups, were the questions predefined?
Mark only one oval.

- o Yes, questions predefined (no flag)
- o No, questions not predefined ("flag")
- o Can't tell/not discussed ("unsure flag")

74. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

75. For interviews and focus groups, was the facilitator/interviewers trained?
Mark only one oval.

- o Yes, trained (no flag)
- o No, not trained ("flag")
- o Can't tell/not discussed ("unsure flag")

76. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

77. Was saturation mentioned?

- o Mark only one oval.
- o Yes, mentioned (no flag)
- o No, not mentioned ("flag")

78. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

79. Was there a description of how the research themes were identified?
Mark only one oval.

- o Yes, description (no flag)
- o No, no description ("flag")

80. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

81. Were the research findings were analyzed by more than one assessor?
Mark only one oval.

- o Yes, more than one (no flag)
- o No, only one ("flag")
- o Can't tell/not discussed ("unsure flag")

82. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

83. Were participant answers reviewed for clarification (i.e., member check)?
Mark only one oval.

- o Yes, reviewed (no flag)
- o No, not reviewed ("flag")
- o Can't tell/not discussed ("unsure flag")

84. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

85. Were sequences from the original data presented (i.e. quotes)?
Mark only one oval.

- o Yes, presented (no flag)
- o No, not presented ("flag")

86. Explanation for rating
If notes for the previous question, please include. If no notes, write "n/a"

Appendix 3-4. A hypothetical model of consumer responses to tobacco products. Taken from Reese et al (26).

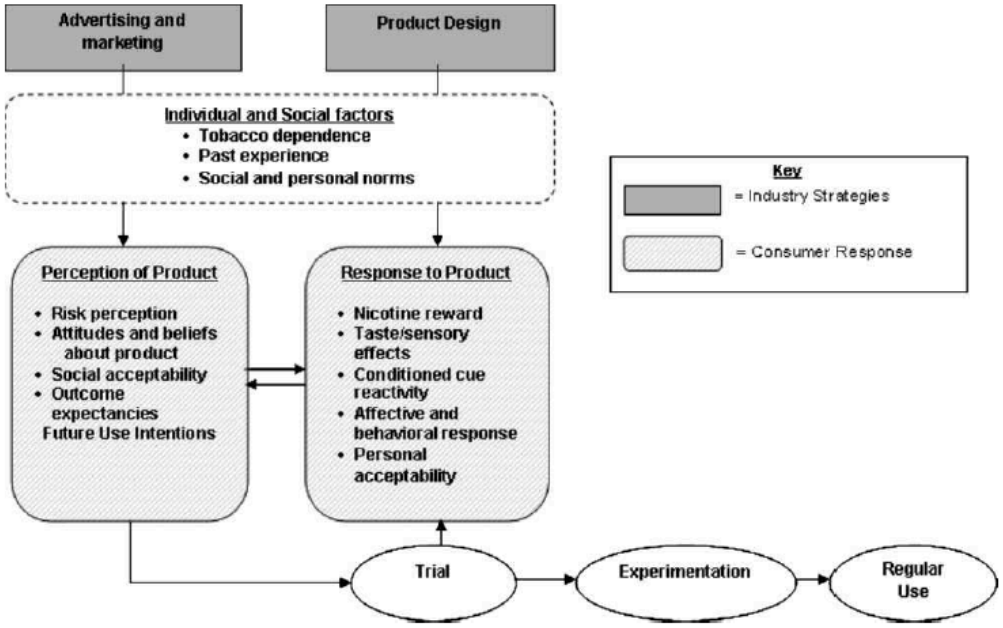

Figure 1. Hypothetical model of tobacco CR.

Figure 3-1. Flowchart of included studies

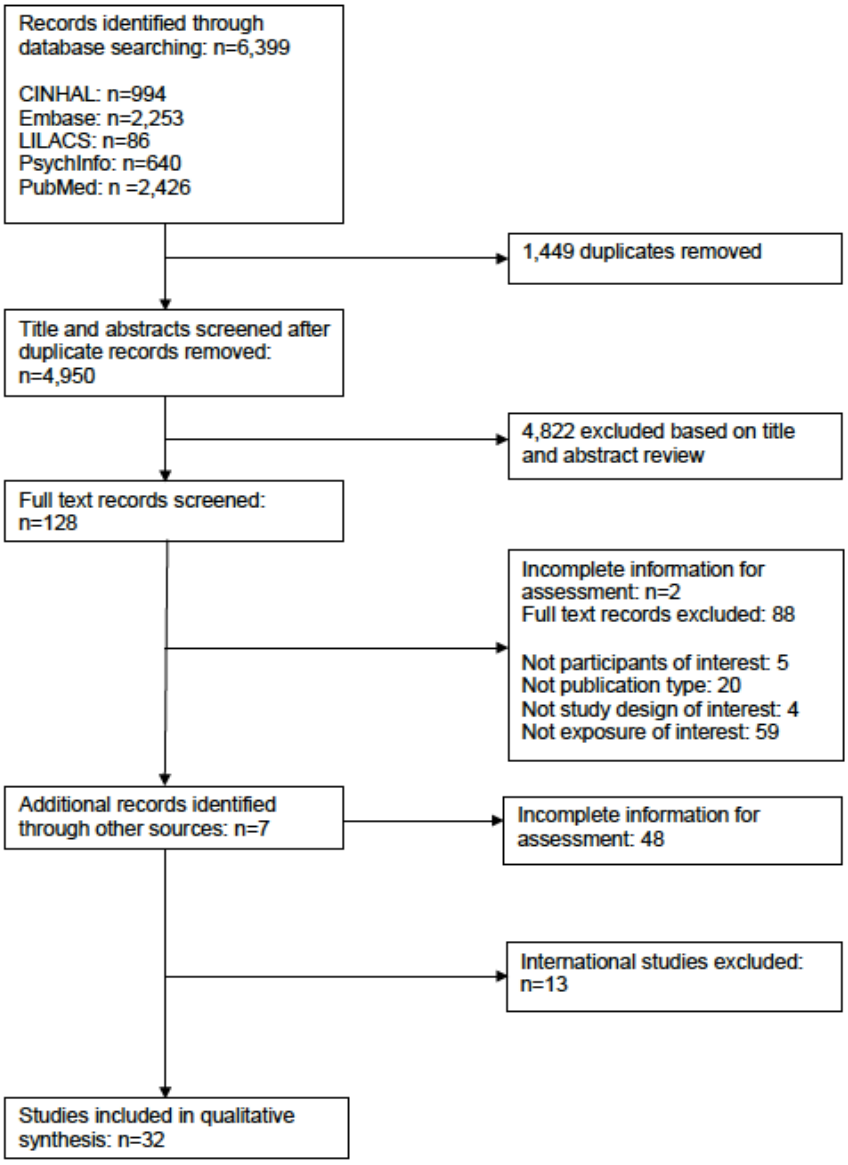

Table 3-1. Sample description and use of nonflavored tobacco products

Study ID (first author, year published)	Study Aim	Flavored Products	Sample Description (When provided: sample size, age range, mean age (SD), % males)	Socioeconomic status Race/Ethnicity		Nonflavored tobacco use % (95% CI)	
Cohort - cross sectional (one time point)							
Aljarrah, 2009	Assess characteristics and perceptions of hookah users in relation to the belief about hookah smoking harmfulness	Hookah	235 hookah café patrons aged 17-35 in and nearby downtown San Diego; mean age 21.8; 57% male	**Race/Ethnicity**		**Cigarettes**	
				African American	6.6%	Yes	28.4%
				Asian	11%	No	71.6%
				Latino	22.4%	**Hookah**	
				Middle Eastern	21.5%	Daily	13.5%
				Other	5.7%	Weekly	35.2%
				White	32.9%	Monthly	24.4%
						Six month	27.0%
Allen, 2003	Summarize tobacco use prevalence estimates from the 2002 NYTS and describe changes in prevalence since 2000	Bidis,* Kreteks	26119 middle and high school students in public and private schools nation-wide	-		**Tobacco**	
						Middle school students	
						2002 - Any current use	13.3% (±1.4)
						2000 - Any current use	15.1%(±1.5)
						High school students	
						2002 - Any current use	28.4%(±1.7)
						2000 – Any current use	34.5%(±1.9)
						Cigarettes	
						Middle school students	
						2002 – Current use	10.1%(±1.2)
						2000 – Current use	11.0%(±1.2)
						High school students	
						2002 – Current use	22.9%(±1.6)
						2000 – Current use	28.0%(±1.7)
						Cigars	
						Middle school students	
						2002 – Current use	6.0%(±0.7)
						2000 – Current use	7.1%(±1.0)
						High school students	
						2002 – Current use	11.6%(±0.9)
						2000 – Current use	14.8%(±1.1)
						Pipes	
						Middle school students	
						2002 – Current use	3.5%(±0.5)
						2000 – Current use	3.0%(±0.4)
						High school students	
						2002 – Current use	3.2%(±0.6)
						2000 – Current use	3.3%(±0.4)
						Smokeless Tobacco	
						Middle school students	
						2002 – Current use	3.7%±0.8
						2000 – Current use	3.6%(±0.9)
						High school students	
						2002 – Current use	6.1%(±1.1)
						2000 – Current use	6.6%(±0.9)

Dawkins, 2013**	Add to the current knowledge of the nature of e-cigarette users, its use, and its effects	E-cigarettes	1347 respondents to an online survey hosted on the University of East London website with links from The Electronic Cigarette Company and Totally Wicked E-Liquid websites; mean age 43.39 (11.99); 70% male	**Education:**		**Cigarettes**	
				Masters/PhD/equiv	14%	Former	83%
				Degree	30%	Current	16%
				Higher teaching qual/equiv	10%	Never	4%
				A level/SCE higher/equiv	13%	**E-cigarettes**	
				O level/GCSE (Grade A-C)/equiv	9%	Ever	100%
				CSE Grade 2-5/0 Levels (Grades D&E)/GCSE(grades D-G)/NVQ level 1	3%		
				CSE undergrad	1%		
				Other	20%		
				Race/Ethnicity			
				Black	<1%		
				Mixed	2%		
				White	96%		
				Asian	1%		
King, 2013	Determine national and state-specific estimates of the prevalence and sociodemographic correlates of flavored cigar smoking among U.S. adults	Cigars	118215 non-institutionalized adults aged ≥18 years who were respondents to the 2009–2010 National Adult Tobacco Survey	-		**Cigars/cigarillos/small cigars**	
						Current	4%
						Ever	6.6% (6.3-7.0)
Klein, 2008	Compare the prevalence of flavored cigarette use among older adolescent and young adult smokers (17–26 years old) and adult smokers aged 25 years and older from two national telephone surveys conducted during 2004 and 2005	Cigarettes	NYSCS: 1444 young adults 17-24 years olds who had smoked at least 20 lifetime cigarettes, and smoked in the previous 30 days; 53.6% male AHCSS: 825 adults aged ≥25 years who smoked at least 100 lifetime cigarettes; 53.7% male	**NYSCS: Race/Ethnicity**		**Cigarettes**	
				Hispanic	9.2%	Current	100%
				Non-Hispanic	9.8%		
				Non-Hispanic White	75.8%		
				Other	5.2%		
				AHCSS: Race/Ethnicity			
				Hispanic	6%		
				Non-Hispanic White	76.8%		
				Non-Hispanic Black	12%		
				Other	5.2%		
Pepper, 2013	Explore awareness of e cigarettes among males ages 11-19 and their willingness to try them.	E-cigarettes	228 adolescent males aged 11-17 who were recruited through their parents, who were members of a panel of U.S. households constructed using random digit dialing and address based sampling; mean age 15.1 (2.1); 100% male	**Household income**		**Cigarettes**	
				<$60000	48%	Nonsmoker	91%
				≥$60000	52%	Smoker	9%
				Parent education		**E-cigarettes**	
				High school or less	44%	0.88%***	
				Some college or more	56%		
				Race			
				Non-white	20%		
				White	80%		
				Ethnicity			
				Hispanic/Latino	17%		
				Non-Hispanic Latino	83%		
Regan,	(1) Determine the proportion of	Cigars	4556 adults aged 18+ who	-		**Dissolvable tobacco**	

2012	adults in this sample who were aware of each of these products; (2) Assess the percentage of adults in this sample who were currently using these products; and (3) Examine the public's beliefs regarding harm caused by use of these products.		completed the 2009 ConsumerStyles survey			Ever Current **Snus** Ever Current	0.5% 0.3% 5.4% 1.8%
Smith-Simone, 2008	Address the lack of knowledge about the about the knowledge, attitudes, beliefs, and smoking patterns of waterpipe users in U.S. young adults	Hookah	Café: 101 tobacco waterpipe users aged 18+, recruited via a flyer posted and circulated in the café, and also by word-of mouth; 71.3% male Internet: 201 respondents aged 18+ to a threat on HookahForum.com; use was not used to determine eligibility, though the forum exists solely for waterpipe tobacco smokers; 80.1% male	**Student status** Student Non student **Years of education** ≤12 years ≥13 years **Race/Ethnicity** Other White 84.6%	 57.0% 43.0% 25.4% 74.6% 15.4% 84.6%	**Tobacco other than hookah/cigarettes** Past month use None **Hookah and cigarettes** Past month **Hookah and other tobacco products** Past month **Cigarettes** Past month No past month **Hookah** Ever use Past month use No past month use *Frequency of use* Yearly Monthly Weekly Daily *Past month frequency* 0-1 times 2-10 times 11-20 times 21+ times *Hookah and no other substance* Past month	 33% 67% 25.9% 20.0% 53.7% 46.3% 100% 94.1% 5.9% 11.5% 28.5% 41.2% 18.8% 18.4% 50.7% 18.4% 12.5% 37.8%
Soldz, 2003	Discuss the prevalence of youth use of cigars, bidis, and kreteks, and characteristics of users	Kreteks	5016 students in grades 7-12 throughout Massachusetts; 48.9% male	**School status** Public and parochial students **Race/Ethnicity** American Indian/Alaskan Native Asian/Pacific Islander Black (not Hispanic) Hispanic/Latino Black (not Hispanic)	 100% 0.6% 3.7% 2.1% 8.4% 2.1%	**Cigarettes** Ever Current **All cigars** Ever Current **Regular cigars** Ever	 33.7% (31.5-36.0) 14.4% (13.0-15.9) 18.2% (16.7-19.9) 5.9% (5.1-6.7) 16.4% (14.9-18.0)

				Other	4.1%	Current	4.7% (4.1-5.4)
						Little cigars/cigarillos	
						Ever	11.9% (10.7-13.2)
						Current	3.4% (2.8-4.0)
						Smokeless tobacco	
						Ever	4.6% (4.0-5.4)
						Current	1.7% (1.3-2.2)
						Bidis	
						Ever	6.5% (5.6-7.5)
						Current	2.3% (1.8-3.1)
Soldz, 2005	Investigate young people's attitudes toward and beliefs about these alternative tobacco products	Kreteks	5016 students in grades 7-12 throughout Massachusetts; 48.9% male	**School status**		**Cigars**	
				Public school students	100%	No use	81.8%
				Race/Ethnicity		Ever	12.3%
				Asian/Pacific Islander	3.7%	Current	5.9%
				Black	2.1%	**Bidis (among those who had heard of bidis)**	
				Hispanic	8.4%	No use	72.0%
				Other	4.6%	Ever	20.2%
				White	81.2%	Current	7.1%
Suftin, 2014	(1) Describe the variety of substances that young adults smoke from hookahs; (2) Determine whether subtypes or classes of hookah users exist based on the types of substances smoked and (3) Describe the correlates associated with these classes	Hookah	1509 undergraduate students attending eight universities (seven public and one private) in North Carolina; 46% male	**Education Status**		**Cigarettes**	
				College student	100%	Never smoker	30%
				Mother's highest education		Former/experimenter	29.0%
				4-year college or higher	57%	Current nondaily	33%
				Some college or less	43%	Current daily	8.0%
				Father's highest education		**Hookah**	
				4-year college or higher	61%	Ever	44%
				Some college or less	52%		
				Race/Ethnicity			
				African American	4%		
				Asian/Pacific Islander	2%		
				Hispanic	4%		
				Other	5%		
				White	86%		
Vander Weg, 2005	Examine the prevalence and correlates of ST use among female Air Force recruits in an attempt to better understand the factors related to ST use in females	Kreteks	9087 female recruits who entered Air Force Basic Military Training from October 1999 to October 2000; mean age 20.2 (2.6); 0% male	**Family income**		**Cigarettes**	
				≤$25000	31%	Daily or occasional	30.4%
				>$25000-$45000	27.3%	**Smokeless tobacco**	
				>$45000-$70000	23.4%	Daily or occasional	0.4%
				>$70000	18.2%	Former	0.2%
				Education		Ever	6.6%
				High school graduate/GED	73.1%		
				Some college	26.9%		
				Race/Ethnicity			

				Asian/Pacific Islander	4.4%		
				Black	25.7%		
				Hispanic	10.3%		
				Native American	1.1%		
				Other	3.6%		
				White	55%		
Vander Weg, 2008	Evaluate the use of several different alternative tobacco products (bidis, cigars, kreteks, pipes, and ST) in a large sample of young adults who are particularly vulnerable to tobacco use given their age and military status.	Kreteks	31107 active duty recruits who entered Air Force Basic Military Training from October 1999 to September 2000; 74.8% male	**Family income**		**Cigarettes**	
				≤$25000	26%	Current	32.7%
				>$25000-$45000	25.9%	**Cigars**	
				>$45000-$70000	25.2%	12.3% (11.8-12.8)	
				>$70000	22.9%	**Pipes**	
				Education		1.1% (0.9-1.2)	
				High school graduate/GED	78.9%	**Smokeless**	
				Some college	21.1%	6.7% (6.3-7.0)	
				Race/Ethnicity		**Bidis**	
				African American	18.7%	2.0% (1.8-2.3)	
				Asian American/Pacific Islander	4%		
				Caucasian	63.5%		
				Hispanic	10.1%		
				Native American	0.8%		
				Other	2.9%		
Villanti, 2013	Identify the prevalence of current flavored tobacco product use, dual use of flavored and menthol products, and sociodemographic predictors of flavored tobacco product use in a nationally representative sample of young adults.	Chew, Cigars, Cigarettes, E-cigarettes, Hookah, Pipes, Snus, Spit, Orbs, Other non-combustible products	982 young adults aged 18–34 years drawn from GfK's Knowledge Panel.® All included participants reported past 30-day use of any tobacco product and provided information on the use of flavored brands	-		**Any tobacco product**	
						Past 30 day	100%
Quasi-experimental and experimental studies							
Ashare, 2007	Investigate college students' expectancies for flavored and non-flavored cigarettes and the degree to which expectancies and smoking status predicted intentions to try a brand	Cigarettes	424 undergraduates an in introductory psychology class; Mean ages for nonsmokers 19.2 (2.2); Susceptible/Experimenter 19.3 (3.4); Regular 19.3 (2.1); 43% male	**Student Status**		**Cigarettes**	
				College students	100%	Nonsmoker	59%
				Nonsmoker		Susceptible/Experimenter	26%
				African American	9%	Regular	15%
				Asian/Pacific Islander	19%		
				Hispanic	5%		
				White, Non-Hispanic	67%		
				Susceptible/Experimenter			
				Asian/Pacific Islander	17%		
				Hispanic	6%		
				White, Non-Hispanic	79%		
				Regular smoker			
				African-American	2%		
				Asian/Pacific Islander	32%		
				Hispanic	9%		

				White, Non-Hispanic	56%		
Cobb, 2011	Compare the subjective effect profile of waterpipe tobacco and cigarette smoking	Hookah	54 healthy individuals aged 18-50 from the Richmond, VA community with no intent to quit smoking; mean age 21.2(2.3); 67% male	**Race/Ethnicity**		**Cigarettes**	
				Non-white	31%	At least 5/wk for past mo.	100%
				White	69%	**Hookah**	
						At least 2/mo. for past 6 mo.	100%
Blank, 2011a	Determine the extent to which the acute effects of waterpipe tobacco smoking were due to nicotine exposure	Hookah	37 healthy, non-regular marijuana users aged 18-50 with no past use of other drugs; mean age 20.5 (12.77); 78.4% male	**Race/Ethnicity**		**Cigarettes**	
				African American	8.1%	Current >5/month	100%
				Asian	18.9%	**Hookah**	
				Caucasian	54.1%	Current 2-5 times/month	100%
				Hawaiin/Pacific Islander	2.7%		
				Mixed/Other Ethnicity	16.2%		
Blank, 2011b	Evaluate the cardiovascular response, toxicant exposure, subjective effects, and puffing topography of Black & Mild cigarillos	Cigars	16 greater Richmond, VA community volunteers aged 18-55; mean age 27.7(10.8); 62.5% male	**Race/Ethnicity**		**Cigarettes**	
				White	31%	Smoker	56%
				Non-white	69%	Nonsmoker	44%
						Cigarillos (Black & Milds)	
						Used 5+ Black & Mild cigarillos/mo. for 6mo or more	100%
						Cigarettes and Cigarillos (Black & Milds)	
						Concurrent use	56%
Malson, 2002	Determine whether smoking bidis, an additive-free cigarette, and conventional cigarettes caused similar biochemical, physiological and subjective effects	Bidis	10 healthy, local community volunteers with a history of bidi use, aged 20-37; mean age 24.5; 90% male	-		**Cigarettes**	
						Current (regular)	100%
Malson, 2003	Compare the changes in exhaled CO, cardiovascular effects, and subjective effects of clove versus conventional cigarettes	Kreteks	10 local community volunteers aged 19-46 who had previous smoked either clove or bidi cigarettes without adverse reactions; mean age 30.3; 70% male	-		**Cigarettes**	
						Current (regular)	100%
						Bidis	
						Ever use	100%
Manning, 2009	Examine the interactive effects of cigarette package flavor descriptors and sensation seeking on adolescents' brand perceptions	Cigarettes	253 high school students at a school in either the central or southeast United States who received parental consent; mean age 15.7; 40% male	**Race/Ethnicity**		**Cigarettes**	
				Southeastern School		*Southeastern School*	
				African American	29%	Past month	26%
				Central School		*Central School*	
				Mexican American	11%	Past month	17%
O'Connor, 2007	Explore differences in puff topography and cigarette ratings between flavored and unflavored Camels among college student smokers	Cigarettes	20 participants aged 18-30 who smoked at least 100 lifetime cigarettes, and were not trying to quit; 50% male	**Student Status**		**Cigarettes**	
				College student	100%	Current nonmenthol	100%
Qualitative							
Choi, 2012	Explore young adults' perceptions of snus, dissolvable tobacco products, and electronic cigarettes and intention to try these products	E-cigarettes, Snus, Orbs, Other non-combustible products	66 residents of the Minneapolis-St. Paul, MN, area aged 18-26 who had either used some tobacco in the past 30 days or could	**School Status**		**Cigarettes**	
				4-y college student or graduate	47%	Past 30 day	70%
				≤ 2-y college student or graduate	53%	No past 30 day	30%

			specify where they had seen tobacco advertisements during the past 30 days; 39% male	**Race/Ethnicity**		**Other combustible products**	
				African American	6%	Past 30 day	15%
				Asian	29%	No past 30 day	85%
				Other	9%	**Smokeless tobacco**	
				White	56%	Past 30 day	3%
						No past 30 day	97%
Griffiths, 2011	Investigate the growing practice of hookah consumption among college students	Hookah	20 college-aged individual, aged 18-23, who have current or past hookah smoking experience; mean age 20.1; 50% male	**Student/Job Status**		**Cigarettes**	
				College student	95%	Smoker	5%
				Receptionist	5%	Socially	10%
				Race/Ethnicity		Occasionally	10%
				African American	10%	Past	10%
				Caucasian	70%	Nonsmoker	65%
				German	5%	**Hookah**	
				Indian	5%	Current or past	100%
				Jamaican	5%		
				Mexican	5%		
Lavo, 2004	Add to the existing body of smokeless tobacco research the personal perspective of adolescents	Chew, Spit, Other non-combustible products	20 adjudicated adolescents aged 15-17 selected from a residential facility in Northeast Pennsylvania; mean age 15.85	**Familial Status**		**Smoke tobacco**	
				Single parent	55%	15%	
				Both parents	40%	**Smokeless tobacco**	
				Other relative	5%	20%	
				Income		**Smoke and smokeless tobacco**	
				An overview shows participants had enough household income to get by		60%	
Liu, 2012	Examine perceptions of traditional and novel smokeless tobacco products and packaging among adolescents and adults	Chew, Snus, Orbs, Other non-combustible products	Smokeless tobacco users in four rural Ohio counties; 23 adolescents and 38 adults; mean ages adolescents 17.2 (0.8); adults 28.9 (12.9); Adolescents 100% male; Adults 100% male	**Education**		**Cigarettes**	
				Adolescents		*Adolescents*	
				<High school	65.2%	Smokers	56.5%
				Missing	34.8%	Nonsmokers	39.1%
				Adults		*Adults*	
				High school of GED	26.3%	Smokers	31.6%
				Some college	68.4%	Nonsmokers	39.1%
				≥College	5.3%	**Smokeless Tobacco**	
				Work for Pay		*Adolescents*	
				Adolescents		</= 5 days per week	43.5%
				Full-time	4.4%	6-7 days/week	43.5%
				Part-time	43.5%	Missing	13%
				No	47.8%	*Adults*	
				Missing	4.4%	<=5 days/week	34.2%
				Adults		6-7 days/week	65.8%
				Full-time	36.8%	*Total sample*	
				Part-time	50%	Current	100%
				No	13.2%		
				Place of Residence			
				Adolescents			
				Live with both parents	21.7%		
				Live with one parent	13%		
				Live with other	30%		
				Missing	35%		
				Household Income			
				Adults			

				<$15000	15.8%		
				$15000-$24999	15.8%		
				$25000-$34999	21.1%		
				$35000-$49999	5.3%		
				≥$50000	31.6%		
				Missing	10.5%		
				Race			
				Adolescents			
				African American	4.4%		
				Missing	4.4%		
				Other	17.4%		
				White	73.9%		
				Adults			
				White	100%		
				Ethnicity			
				Adolescents			
				Non-Hispanic	78.3%		
				Hispanic	17.4%		
				Missing	4.4%		
				Adults			
				Hispanic	2.6%		
				Non-Hispanic	97.4%		
Richter, 2008	Learn the appeal of nontraditional tobacco product and understand factors related to their use	Hookah,* cloves	137 young adult smokers aged 18-22 in Dallas, Texas and Chattanooga, Tennessee who had tried or used nontraditional tobacco products	**Student Status**		**Cigarettes**	
				College students	50%	Current	100%
				Non-college students	50%	**Cigars**	
				Race/Ethnicity		Ever (Swisher Sweets)	87%
				African Americans	26%	Ever (Black & Mild)	96%
				Hispanics	23%	**Bidis**	
				Non-Hispanic Whites	51%	Ever	23%
Sifaneck, 2005	Explore reasons for selection of different tobacco products available in the legal commercial market	Cigars	92 marijuana/blunt users aged 14-35 who are residents of New York City neighborhoods and are diverse with regard to age, race/ethnicity, gender and class/neighborhood; 57% male	**Race/Ethnicity**		**Cigar-for-blunts**	
				African American	24%	100%	
				Asian	14%		
				Latino	19%		
				Other	11%		
				White	32%		
Other							
Oliver,	Examine the choice of brand flavor	Smokeless	Overall sample: 468	-		**Smokeless tobacco**	

2013	in the course of ST product use, from initiation to regular use, in an intervention seeking population; examine whether users of flavored ST products differ from nonflavored users on a number of characteristics	tobacco products	smokeless tobacco users aged 18-70; mean ages: mean ages no flavor smokeless tobacco use 37.3(7.7); flavor tobacco use 32.5(7.8) Studies 1-4: Adult smokeless tobacco users who were interested in reducing use but not quitting; Study 1: only recruited those who were using Copenhagen or Kodiak Wintergreen brand smokeless tobacco products. Study 5: smokeless tobacco users, regardless of their desire to reduce or quit.		Current (specifically nonflavored)	41.2%
Case report/case series						
Al-Saieg, 2007	Analyze cases of acute eosinophilic pneumonia following smoking of flavored cigars for characteristic features	Cigars	Two patients aged 23 and 53 who presented at a hospital in Youngtown, OH; 100% male	-	-	
CDC, 1985	Describe examples of severe illnesses possibly resulting from smoking clove cigarettes	Kreteks	Two patients aged 19 and 16 who presented at a hospital in California; 100% male	-	-	
Guidotti, 1989	Describe a patient in whom, after she smoked a clove cigarette, pneumonia complicated by lung abscess developed	Kreteks	One patient aged 18 who presented at a hospital, unspecified location; 0% male	-	-	

*Product was described by authors as being flavored, but question was not given confirming that participants were asked about the flavored version of these products
**Data was collected with participants recruited within the United States, as well as internationally. Results are not segmented by country.

Table 3-2. Use of flavored tobacco products

Study ID (first author, year published)	Sample	Measures/Analysis	Age (years) or Population	% (95% CI)	Result
Section 1: Flavored Tobacco Use, Assessed by Age					
King, 2013	2009-2010 National Adults Tobacco Survey	Past 30 day flavored cigar smoking among ever cigar smokers	18-24 25-44 45-64 ≥65 All	9.1 (7.8–10.5) 3.1 (2.7–3.6) 1.4 (1.2–1.7) 0.2 (0.1–0.3) 2.8 (2.6-3.1)	No statistical test performed
King, 2013	2009-2010 National Adults Tobacco Survey	Past 30 day flavored cigar smoking among current cigar smokers	18-24 25-44 45-64 ≥65 All	57.1 (51.4–62.5) 43.2 (38.7–47.8) 28.9 (25.1–33.2) 13.4 (9.3–18.9) 42.9 (40.1-45.7)	No statistical test performed
Klein, 2008	National Youth Smoking Cessation Survey	Chi-squared test for independence, past 30 day use of any flavored cigarette (Camel Exotic Blends, Kool Smooth Fusion, Salem Silver Label), by age	17 18-19 20-21 22-23 24-26 All	22.8 (14.8–33.4) 21.7 (17.1–27.3) 10.1 (7.4–13.6) 8.8 (6.1–12.6) 9.0 (6.2–13.1) 11.9 (10.2-13.8)	Age significantly associated with any flavored tobacco use (**p<.001**)
Klein, 2008	National Youth Smoking Cessation Survey	Chi-squared test for independence, past 30 day use of Camel Exotic Blends, by age	17 18-19 20-21 22-23 24-26 All	15.8 (9.2–25.8) 19.4 (15.0–24.7) 9.8 (7.2–13.3) 8.3 (5.6–12.1) 7.5 (4.9–11.3) 10.5 (8.9-12.3)	Age significantly associated with any flavored tobacco use (**p<.01**)
Klein, 2008	National Youth Smoking Cessation Survey	Chi-squared test for independence, past 30 day use of Kool Smooth Fusion Cigarettes, by age	17 18-19 20-21 22-23 24-26 All	3.6 (1.3–9.5) 2.7 (1.2–5.9) 0.7 (0.2–2.3) 0.5 (0.1–2.0) 0.7 (0.2–2.9) 1.1 (0.7-1.8)	Chi-squared test for independence produced non-significant results
Klein, 2008	National Youth Smoking Cessation Survey	Chi-squared test for independence, past 30 day use of Salem Silver Label Cigarettes, by age	17 18-19 20-21 22-23 24-26 All	6.5 (2.8–14.3) 2.2 (1.0–4.7) 1.3 (0.6–2.9) 1.4 (0.6–3.4) 1.5 (0.6–3.8) 1.8 (1.2-2.7)	Chi-squared test for independence produced non-significant results
Klein, 2008	Assessing Hardcore Smoking Survey	Chi-squared test for independence, past 30 day use of any flavored cigarette (Camel Exotic Blends, Kool Smooth Fusion, Salem Silver Label) by age	25-39 40-54 >55	11.2 (5.9–20.4) 6.2 (3.3–11.1) 0.8 (0.2–2.4)	Age significantly associated with any flavored tobacco use (**p<.01**)

Klein, 2008	Assessing Hardcore Smoking Survey	Chi-squared test for independence, past 30 day use of Camel Exotic Blends, by age	25-39 40-54 >55	9.1 (4.1–19.0) 5.0 (2.4–10.0) 0.8 (0.2–2.4)	Age significantly associated with any flavored tobacco use (**p<.05**)
Klein, 2008	Assessing Hardcore Smoking Survey	Chi-squared test for independence, past 30 day use of Kool Smooth Fusion Cigarettes, by age	25-39 40-54 >55	0.9 (0.3–2.6) 0.1 (0.0–0.9) 0.3 (0.0–1.8)	Chi-squared test for independence produced non-significant results
Klein, 2008	Assessing Hardcore Smoking Survey	Chi-squared test for independence, past 30 day use of Salem Silver Label Cigarettes, by age	25-39 40-54 >55	2.1 (0.9–4.4) 1.2 (0.4–3.4) 0.0 (—)	Chi-squared test for independence produced non-significant results
Oliver, 2013	Data drawn from five studies	Current mean age; mixed-effects analysis of variance model, fitted with flavor (yes, no) as a fixed effect and a random effect for individual study; looks at current smokeless product (flavored/nonflavored)	 Mint-flavored user Nonflavored user	*Mean age (SD)* 32.5 (7.8) 37.3 (7.7)	**p<0.0001**
Oliver, 2013	Data drawn from five studies	Mean age of first dip; mixed-effects analysis of variance model, fitted with flavor (yes, no) as a fixed effect and a random effect for individual study; looks at current smokeless product (flavored/nonflavored)	 Mint-flavored user Nonflavored user	*Mean age (SD)* 16.3 (5.5) 16.8 (5.4)	p=0.358
Oliver, 2013	Data drawn from five studies	Mean age of daily regular use; mixed-effects analysis of variance model, fitted with flavor (yes, no) as a fixed effect and a random effect for individual study; looks at current smokeless product (flavored/nonflavored)	 Mint-flavored user Nonflavored user	*Mean age (SD)* 19.6 (5.7) 19.5 (5.9)	p=0.941
Soldz, 2003	Cigar Use Reasons Evaluation	Mean age of initiation by product; "robust test of the significant of mean differences in these ages among participants reporting lifetime use of both forms of tobacco"	 Kreteks Cigarettes	*Mean age (SD)* 14.08 (1.73) 12.64 (1.92)	Difference in mean (SE) = 1.69 (0.10). **p<0.001**
Soldz, 2003	Cigar Use Reasons Evaluation	Mean age of initiation by product; "robust test of the significant of mean differences in these ages among participants reporting lifetime use of both forms of tobacco"	 Kreteks Cigars	*Mean age (SD)* 14.08 (1.73) 13.47 (1.80)	Difference in mean (SE) = 0.67 (0.10). **p<0.001**
Soldz, 2003	Cigar Use Reasons Evaluation	Mean age of initiation by product; "robust test of the significant of mean differences in these ages among participants reporting lifetime use of both forms of tobacco"	 Kreteks Bidis	*Mean age (SD)* 14.08 (1.73) 13.90 (1.95)	Difference in mean (SE) = 0.10 (0.11). Difference in means not significant.
Vander Weg, 2008	Survey to assess alternative forms of tobacco use in a population of young adult military recruits	Multivariable logistic regression; model includes gender, race and ethnicity, educational attainment, income and marital status; looks at current use of kreteks by age	<20 years old ≥20 years old Total	2.9% (2.6–3.2) 3.2% (2.8–3.6) 3.0 (2.7-3.2)	No significant association found
Villanti,	Legacy Young Adult	Multivariable logistic regression of any current			*OR (95% CI)*

2013	Cohort Study, Wave 2	flavored tobacco use compared to no flavored tobacco use; controls for gender, race/ethnicity, education and use of any menthol-brand tobacco product	18-24 25-34	N/R	**1.89 (1.14-3.11) (p<0.05)** 1.0 Referent
Villanti, 2013	Legacy Young Adult Cohort Study, Wave 2	Bivariate analysis of flavored tobacco product use by age	18-24 25-34	N/R	Younger age was a predictor of flavored tobacco product use
Section 2: Flavored Tobacco Use, Assessed by Tobacco Use Status					
Oliver, 2013	Data drawn from five studies	Z-test comparing percent of users who started with a nonflavored product and now use a flavored product with percent of users who started with a flavored product and now use a nonflavored product	Users who started with a nonflavored product and now use a flavored product Users who started with a flavored product and now use a nonflavored product	51.3 35.6	ST users who started by using nonflavored products were more likely to switch to mint-flavored products compared with the other way around (**p<.0001**). No coefficient given.
Oliver, 2013	Data drawn from five studies	Z-test comparing percent of users who started with a nonflavored product and now use a nonflavored product with percent of users who started with a flavored product and now use a flavored product	Users who started with a nonflavored product and now use a nonflavored product Users who started with a flavored product and now use a flavored product	48.7 64.4	ST users who started with a mint-flavored product were more likely to currently use a mint-flavored product compared with those who continue with nonflavored products (**p=.001**). No coefficient given.
Soldz, 2003	Cigar Use Reasons Evaluation	Smoking initiation precedence among users of kreteks and cigars	Initiated with kreteks Initiated with cigars Initiated both at same age	17.8 (13.5-23.0) 49.7 (43.9-55.4) 32.5	N/A
Soldz, 2003	Cigar Use Reasons Evaluation	Smoking initiation precedence among users of kreteks and bidis	Initiated with kreteks Initiated with bidis Initiated both at same age	23.9 (17.8-31.2) 30.1 (24.0-37.1) 46	N/A
Soldz, 2003	Cigar Use Reasons Evaluation	Smoking initiation precedence among users of kreteks and cigarettes	Initiated with kreteks Initiated with cigarettes Initiated both at same age	7.5 (5.3-10.6) 71.7 (67.0-75.9) 20.8	N/A
Soldz, 2003	Cigar Use Reasons Evaluation	Current kretek use, by cigarette use	Current cigarette smokers Ever cigarette smokers	75.8 (67.0-82.8) 94.5 (88.9-97.3)	N/A
Soldz, 2003	Cigar Use Reasons Evaluation	Ever kretek use, by cigarette use	Current cigarette smokers Ever cigarette smokers	61.6 (56.6-66.5) 90.8 (87.8-93.2)	N/A
Vander Weg, 2005	Female military recruits	Simple odds ratio (unadjusted) looking at ever use of kreteks versus never use	 Lifetime smokeless tobacco use Never smokeless tobacco use		*OR (95% CI)* 4.49 (3.79-5.31), **p<.001** 1.0 Referent

Vander Weg, 2005	Female military recruits	Multivariate odds ratio (adjusted) looking at ever use of kreteks versus never use	Lifetime smokeless tobacco use Never smokeless tobacco use		*OR (95% CI)* 1.23 (1.01-1.49), **p=.04** 1.0 Referent
Vander Weg, 2008	Survey to assess alternative forms of tobacco use in a population of young adult military recruits	Univariate logistic regression looking at use of kreteks	Cigarette smokers Non-cigarette smokers		*OR (99% CI)* 10.53 (8.41-13.20), **p<.001** 1.0 Referent
Villanti, 2013	Legacy Young Adult Cohort Study, Wave 2	Multivariable logistic regression of any current flavored tobacco use compared to no flavored tobacco use; controls for gender, race/ethnicity, and education	Any menthol use No menthol use	N/R	*OR (95% CI)* 2.28 (1.42-3.67), **p<0.001** 1.0 Referent
Section 3: Flavored Tobacco Use, Overall or by Other Measures of Prevalence					
Allen, 2003	2000 National Youth Tobacco Survey	Current use of kreteks	Middle school students (grades 6-8) High school students (grades 9-12)	2.1 (±0.4) 4.2 (±0.5)	N/A
Allen, 2003	2000 National Youth Tobacco Survey	Current use of bidis*	Middle school students (grades 6-8) High school students (grades 9-12)	2.4 (±0.4) 4.1 (±0.4)	N/A
Allen, 2003	2002 National Youth Tobacco Survey	Current use of kreteks	Middle school students (grades 6-8) High school students (grades 9-12)	2.0 (±0.3) 2.7 (±0.5)	N/A
Allen, 2003	2002 National Youth Tobacco Survey	Current use of bidis*	Middle school students (grades 6-8) High school students (grades 9-12)	2.4 (±0.3) 2.6 (±0.5)	N/A
Malson, 2003	Local community volunteers	Ever use of kreteks	10 local community volunteers aged 19-46 who had previous smoked either clove or bidi cigarettes without adverse reactions	40	
Manning, 2009	High school students at a school in either the central or southeast United States	Smokes flavored cigarettes at least once in a while	High school students; mean age 15.7	19	
Oliver,	Data drawn from five	Current mint flavor use – smokeless tobacco		55.8	

2013	studies				
Oliver, 2013	Data drawn from five studies	Ever mint flavor use – smokeless tobacco		79.4	
Regan, 2012	ConsumerStyles	Ever use of flavored cigarettes	Adults aged ≥18 years, nationally representative, who had heard of flavored cigarettes	27.4 (20.9-33.9)	N/A
Regan, 2012	ConsumerStyles	Ever use of flavored little cigars	Adults aged ≥18 years, nationally representative, who had heard of flavored cigars	31.5 (27.3-35.7)	N/A
Richter, 2008	Young adult smokers aged 18-22 in Dallas, Texas and Chattanooga, Tennessee who had tried or used nontraditional tobacco products	Ever use of hookah	Young adult smokers aged 18-22 in Dallas, Texas and Chattanooga, Tennessee who had tried or used nontraditional tobacco products	4	
Richter, 2008	Young adult smokers aged 18-22 in Dallas, Texas and Chattanooga, Tennessee who had tried or used nontraditional tobacco products	Ever use of kreteks	Young adult smokers aged 18-22 in Dallas, Texas and Chattanooga, Tennessee who had tried or used nontraditional tobacco products	4	
Soldz, 2003	Cigar Use Reasons Evaluation	Ever use of kreteks	Middle and high school students from 12 school districts across Massachusetts	8.9 (7.8-10.1)	N/A
Soldz, 2003	Cigar Use Reasons Evaluation	Current use of kreteks	Middle and high school students from 12 school districts across Massachusetts	3.1 (2.4-3.9)	N/A
Soldz, 2005	Cigar Use Reasons Evaluation	Never use of kreteks	Middle and high school students from 12 school districts across Massachusetts who had heard of kreteks/cloves	70.7	N/A
Soldz, 2005	Cigar Use Reasons Evaluation	Ever use of kreteks	Middle and high school students from 12 school districts across	20.1	N/A

			Massachusetts who had heard of kreteks/cloves		
Soldz, 2005	Cigar Use Reasons Evaluation	Current use of kreteks	Middle and high school students from 12 school districts across Massachusetts who had heard of kreteks/cloves	8.1	N/A
Sutfin, 2014	Online survey, part of the Study to Prevent Alcohol-Related Consequences	Ever use of hookah	Students from eight colleges in North Carolina reporting ever smoking tobacco from a hookah	90	N/A
Vander Weg, 2008	Survey to assess alternative forms of tobacco use in a population of young adult military recruits	Ever use of kreteks	Young adult military recruits	24.8	
Villanti, 2013	Legacy Young Adult Cohort Study, Wave 2	Current use of cigars/cigarillos/bidis	18-34 year olds, nationally representative sample	35% (95% CI: 25-47)	
Villanti, 2013	Legacy Young Adult Cohort Study, Wave 2	Current use of cigarettes	18-34 year olds, nationally representative sample	1% (95% CI: 0.00-0.02)	
Villanti, 2013	Legacy Young Adult Cohort Study, Wave 2	Current use of cigars	18-34 year olds, nationally representative sample	13% (95% CI: 0.08-0.21)	
Villanti, 2013	Legacy Young Adult Cohort Study, Wave 2	Current use of pipes	18-34 year olds, nationally representative sample	38% (95% CI: 18-63)	
Villanti, 2013	Legacy Young Adult Cohort Study, Wave 2	Current use of chewing tobacco	18-34 year olds, nationally representative sample	6% (95% CI: 2-18)	
Villanti, 2013	Legacy Young Adult Cohort Study, Wave 2	Current use of dip/snuff	18-34 year olds, nationally representative sample	8% (95% CI: 3-21)	
Villanti, 2013	Legacy Young Adult Cohort Study, Wave 2	Current use of dissolvable tobacco	18-34 year olds, nationally representative sample	13% (95% CI: 2-49)	
Villanti, 2013	Legacy Young Adult Cohort Study, Wave 2	Current use of hookah	18-34 year olds, nationally representative sample	50% (95% CI: 36-64)	
Villanti, 2013	Legacy Young Adult Cohort Study, Wave 2	Current use of e-cigarettes	18-34 year olds, nationally representative sample	13% (95% CI: 6-27)	

* Product was described by authors as being flavored, but question was not given confirming that participants were asked about the flavored version of these products

Table 3-3. Tobacco flavor preference, by product

Study ID (first author, year published)	Type of Product	Measure	Result
Aljarrah, 2009	Hookah	Favorite hookah tobacco flavor	Mint (22%), combination of fruit flavors (19%), individual fruit flavors (most were less than 5%).
Blank, 2011	Hookah	Preferred waterpipe flavor	Apple/double apple (n = 8, 22%), mint (n=6, 16%), strawberry (n = 6, 16%), mango (n = 4, 11%), peach (n = 3, 8%), cherry (n = 2, 5%), watermelon (n = 2, 5%), grape (n=1, 3%), mixed fruit (n=1, 3%), orange (n=1, 3%), guava (n=1, 3%), rose (n=1, 3%), vanilla (n=1, 3%).
Cobb, 2011	Hookah	Preferred waterpipe flavor	Fruit flavors (e.g. mango, strawberry and melon) (n=46, 85%), mint (n=4, 7%), vanilla (n=2, 4%), X on the beach (n=1, 2%), jasmine (n=1, 2%)
Smith-Simone, 2008	Hookah	Favorite flavor of tobacco	"Apple" (n=31, 15.7%), "Other fruit" (n=75, 38.1%), "Mint" (n=18, 9.1%), "No particular flavor" (n=30, 15.2%), "Other flavor" (n=43, 21.8%).
Smith-Simone, 2008	Hookah	Type of tobacco favored	95.9% of participants favored "flavored" tobacco. 4.1% of participants favored "sometimes flavored or not flavored" tobacco.
Blank, 2011	Cigars	Preferred Black & Mild cigarillo flavor	Regular (n=9, 56%), wine (n=7, 44%)
O'Connor, 2007	Cigarettes	Flavor choice	Seven Exotic Blends were offered. The most popular were: Twist (a citrus flavor) (n=7, 35%), Dark Mint (n=4, 20%), Warm Winter Toffee (n=3, 15%), Izmir Stinger (n=3, 15%), Mandarin Mint (n=2, 10%), and Crema (n=1, 1%). No significant differences in outcome measures were noted between Twist and the other flavored varieties (p values>.50).
Dawkins, 2012**	E-cigarettes	Preferred e-cigarette flavor	Participants could endorse more than one option. Favorite flavors among the entire sample were: tobacco (n=664, 53%), fruit (n=421, 33%), mint/menthol (n=357, 28%), chocolate/sweet flavor (n=231, 18%), coffee (n=167, 13%), other (n=196, 16%), vanilla (n=156, 12%), alcohol related (n=49, 4%) and flavorless (n=11, 1%). Current smokers and ex-smokers did not differ with respect to their flavor preference.

Table 3-4. Perception of product

Response domain	Study ID (first author, year published)	Measure	Analytic Approach	Main Results
Attitudes and beliefs about product	Manning, 2009	Hedonic beliefs, measured with a multi-item scale assessing the likelihood that the brand is enjoyable, relaxing and good tasting	2 (descriptor: flavored vs. traditional) x2 (sensation seeking: high vs. low) x2 (school location) x3 (brand) repeated measures ANCOVA model, with brand as the only within-participants factor	There was a significant main effect of package descriptor (F (1, 215) =18.36, p,0.001). The flavor descriptors (M=3.50) led to more positive beliefs about the hedonic qualities of the brands than the traditional descriptors (M=2.64). This effect was qualified by a significant interaction between package descriptor and sensation seeking (F (1, 215) =10.17, p=0.002). Among lower sensation seekers, hedonic brand beliefs did not differ between the two package descriptor conditions (p=0.32; MTraditional=2.81, MFlavor=3.03). Within the higher sensation-seeking group, the flavor descriptors (M=3.98) led to more favorable hedonic brand beliefs than the traditional descriptors (M=2.47; p,0.001).
		Brand attitude, measured with a multi-item scale assessing perceptions from the point of view of another person (such as an acquaintance or friend)		There was a significant interaction between package descriptor and sensation seeking (F (1, 211)=10.47, p<.001). A contrast revealed a marginally significant effect (p=0.10) of the cigarette descriptor within the lower sensation-seekers' condition such that attitudes were more favorable among those exposed to the traditional descriptors (M=2.91) than the flavor descriptors (M=2.53). A second contrast revealed a significant effect (p=0.003) of the descriptor manipulation among higher sensation seekers with brand attitudes being more favorable among those exposed to the flavor than the traditional descriptors (MTraditional=2.40, MFlavor=3.44).
	Soldz, 2005	Kreteks taste good	Contingency table techniques	Endorsement of this statement increased monotonically and significantly (p<0.001) by smoking status: No use 2.0% (95% CI: 1.3-2.9); Lifetime use 69.6% (95% CI: 64.1-74.6); Current use 86.4% (95% CI: 79.1-91.4) Endorsing this item was found to predict use of kreteks (OR=98.77, 95% CI: 35.19-277.23).
		Kreteks smells good		Endorsement of this statement increased monotonically and significantly (p<0.001) by smoking status: No use 9.1% (95% CI: 7.4-11.1); Lifetime use 67.6% (95% CI: 62.2-72.6); Current use 81.6% (95% CI: 73.9-87.4)
		Kreteks are more natural than cigarettes		Endorsement of this statement increased monotonically and significantly (p<0.001) by smoking status: No use 7.9% (95% CI: 6.5-9.6); Lifetime use 34.2% (95% CI: 29.4-39.4); Current use 54% (95% CI: 45.1-62.7)
Future use intentions	Ashare, 2009	Relationship between positive expectancies and willingness to try flavored and nonflavored cigarettes	Logistic regression analysis of "Intention to Try" as a function of smoking status, positive expectancies and negative expectancies	Across all brands, positive expectancies significantly predicted the likelihood one would try a brand. Odds ratios indicated that as positive expectancies increased one point, participants were 1.6 (95% CI: 0.6-1.0, p<0.01, for Salem Regular), 2 (95% CI: 1.4-2.7, p<0.001, for Salem Silver), 1.8 (95% CI: 1.3-2.5, p<0.001, for Camel Light), and 2.4 (95% CI: 1.7-3.4, p<0.001, for Camel Exotic) times more willing to try that particular brand.
		Relationship between negative expectancies and intention to try flavored and nonflavored cigarette brands		Negative expectancies were not reliably related to intention to try Camel Light, Camel Exotic, or Salem Silver. Negative expectancies predicted a modest reduction in intention to try Salem Regulars (OR 0.08, 95% CI: 0.6-1.0, p<0.05).

	Manning, 2009	Trial intentions, measured with a single item, a scale anchored by "very unlikely" (1) and "very likely" (7) that asked participants "In the future, how likely is it that your friends with try [brand name] cigarettes?	2 (descriptor: flavored vs. traditional) x2 (sensation seeking: high vs. low) x2 (school location) x3 (brand) repeated measures ANCOVA model, with brand as the only within-participants factor	The only other significant effect was an interaction between package descriptor and sensation seeking (F(1, 215)=8.92, p=0.003). In assessing the interaction, a contrast revealed that among lower sensation seekers trial intentions were marginally greater in the traditional descriptor condition (M=3.19) than the flavor descriptor condition (M=2.77; p=0.07). Among the higher sensation seekers, the flavored descriptors (M=3.36) led to higher trial intentions than the traditional descriptors (M=2.53; p=0.01).
	Pepper, 2013	Participants were asked: "If one of your best friends were to offer you an e-cigarette, would you try it?" and "If one of your best friends were to offer you a flavored e-cigarette (chocolate, mint, apple, etc.), would you try it?"	Logistic regression	13.2% of participants answered that they were "probably" or "definitely" willing to try both types of e-cigarettes. 3.9% of participants answered that they were "probably" or "definitely" willing to try the flavored e-cigarettes, but not the e-cigarettes that were not specifically described as "flavored." 1.3% answered that they were "probably" or "definitely" willing to try the e-cigarettes that were not specifically described as "flavored," but not the flavored e-cigarettes. The difference between the number of participants willing to try a flavored e-cigarette versus the number willing to try an e-cigarette that was not described as "flavored" did not significantly differ (p=.15).
	Soldz, 2005	Kreteks are something different to try	Contingency table techniques	Endorsement of this statement increased monotonically and significantly (p<0.001) by smoking status: No use 10.8% (95% CI: 9.0-12.8); Lifetime use 60.6% (95% CI 54.7-66.2); Current Use 79.0% (95% CI: 70.5-85.6). Endorsing this item was found to predict use (OR=3.15, 95% CI: 1.63-6.06).
Outcome expectancies	Asahre, 2007	Positive expectancies around flavored (Salem Silver, Camel Exotics) cigarette brands compared to nonflavored (Salem Regular, Camel Lights) cigarette brands Negative expectancies around flavored and nonflavored cigarette brands; intention to try flavored and nonflavored cigarette brands.	Repeated measures ANOVAs (3 Smoking Status x 4 Brand Types). Smoking status was a between-subjects factor and brand was a within-subjects factor	Positive expectancies were influenced by flavor, with higher positive expectancies for Salem Silver compared to Salem Regular across smoking status (brand F(1,421)=155.6, p<0.001, partial η2 =0.27; Salem Silver vs. Regular x Smoking Status, F<1). Similarly, Camel Exotics produced greater positive expectancies than did Camel Lights (brand F(1,421)=38.4, p<0.001, partial η2 =0.08). This difference was at least as strong among susceptible/experimenters (M=0.45, F(1,109)=30.6, p<0.01, partial η2 =0.22) as it was for regular smokers (M=0.43, F(1,63)=8.6, p<0.0, partial η2 =0.12), with only a modest effect among committed nonsmokers (M=0.14, F(1,249)=5.4, p<0.05, partial η2 =0.02; Camel Exotic vs. Light x Smoking Status F(2,421)=4.9, p<0.01, partial η2=0.02) Across all groups, Camel Lights were rated more negatively than were Camel Exotics (F(1,421)=8.2, p<0.01, partial η2 =0.02), an effect that did not reliably vary by smoking status (F(2,421)=2.0, p=0.11). For Salem, the non-flavored product was also rated more negatively than the flavored product; however, this effect was reliable among the nonsmoker and susceptible/experimenter groups (F(1,249)=37.6, pb0.01, partial η2=0.13 and F(1,109)=10.1, p<0.01, partial η2 =0.09, respectively; Salem vs. Salem Silver x Smoking Status F(2, 421)=3.3, p<0.05), but not the regular smokers (F<1).
	Soldz, 2005	Kreteks give you a good buzz	Contingency table techniques	Endorsement of this statement increased monotonically and significantly (p<0.001) by smoking status, from No use 2.3% (95% CI: 1.5-3.4); Lifetime use 21.4% (95% CI: 17.1-26.3): Current use 33.1% (95% CI: 24.6-42.8)

Risk Perception	Soldz, 2005	Kreteks are not as bad for you as cigarettes	Contingency table techniques	Endorsement of this statement increased monotonically and significantly ($p<0.001$) by smoking status, from no use (3.6%, 2.6-4.9) to lifetime use (15.1%, 11.3-19.9) to past month use (28.8%, 21.2-37.8).
Social acceptability	N/R			

Table 3-5. Response to product

Response domain	Study ID (first author, year published)	Measure	Comparators*				Significance
Nicotine reward	Malson, 2002		**Irie Bidi (strawberry)**	**American Spirit ®**	**Sher Bidi**	**Own Brand**	**F-test**
		High in nicotine	4.7 ± 1.8	5.2 ± 1.7	4.2 ± 1.9	5.2 ± 1.1	No differences
Taste/sensory effects	Malson, 2002		**Irie Bidi (strawberry)**	**American Spirit ®**	**Sher Bidi**	**Own Brand**	**F-test**
		Liking	4.8 ± 0.9[a]	3.1 ± 2.2[a]	3.9 ± 1.6	6.3 ± 0.7	F[3,27] = 11.23, p<0.001
		Satisfaction (DSQ)	4.8 ± 1.3[a]	3.1 ± 2.2[a]	3.7 ± 1.7[a]	6.3 ± 0.7	F[3,27] = 10.68, p<0.001
		Satisfaction (maximum=14)[b] (CES)	9.2 ± 2.4[a]	6.1 ± 4.3[a]	8.4 ± 3.4[a]	12.6 ± 1.2	F[3,27] = 9.11, p<0.001
		Enjoyment of sensations in throat and chest	4.7 ± 1.1	2.8 ± 1.8[a]	3.7 ± 1.8[a]	5.7 ± 0.1	F[3,27] = 7.16, p<0.001
		Strength (maximum=35)[b]	21.4 ± 5.4	22.3 ± 9.3	18.6 ± 5.9[a]	24.6 ± 7.4	Not reported
		Craving relief	4.7 ± 1.8[a]	5.4 ± 2.0	4.1 ± 2.0[a]	6.0 ± 0.9	F[3,27] = 3.88, p<0.05
	Malson, 2003		**Clove Cigarette**			**Own Brand**	**Dependent t-test**
		Liking of taste	6.1±0.5			4.8±0.4	t(9)=2.25, P<.05
		Reduction in hunger for food	2.1±1.5			3.0±1.9	t(9)=2.1, P<.10
	O'Connor, 2007		**Exotic**	**Light**			**F-test**
		Liking	3.0 (0.2)	4.5 (0.2)			F[1,18] = 3.8, p=.07
		Satisfaction (DSQ)	4.2 (0.3)	4.2 (0.3)			F[1,18] = 0.3, p=.88
		Strength (maximum=35)[b]	19.1 (1.)	18.3 (1.0)			F[1,18] = 0.8, p=.40
		Harshness/irritation/strength scale[b]					F[1,18] = 11.9, p=.003
		Lights smoked first	12.7 (1.0)	9.1 (1.0)			
		Exotics smoked first	9.2 (1.0)	10.6 (1.0)			
Conditional cue reactivity	N/R						
Affective and behavioral response	Malson, 2002		**Irie Bidi (strawberry)**	**American Spirit ®**	**Sher Bidi**	**Own Brand**	**F-test**
		Psychological reward (maximum=35)[b]	17.5 ± 5.4	13.2 ± 6.5	14.3 ± 7.3	19.3 ± 6.5	F[3,27] = 2.86, p=0.056
Personal acceptability	Malson, 2002		**Irie Bidi (strawberry)**	**American Spirit ®**	**Sher Bidi**	**Own Brand**	**F-test**
		Similar	1.9 ± 1.1[a]	2.1 ± 1.3[a]	1.6 ± 1.0[a]	7.0 ± 0.0	F[3,27] = 84.84, p<0.001
		Aversion (maximum=14)[b]	6.1 ± 3.5	6.0 ± 2.5	4.3 ± 2.1	3.5 ± 1.8	No differences
	Malson, 2003		**Clove Cigarette**			**Own Brand**	**Dependent t-test**
		Different from own brand	1.9±1.2			6.5±1.3	t(9)=10.2, P<.001
	O'Connor, 2007		**Exotic**	**Light**			**F-test**
		Similar	2.8 (0.3)	4.2 (0.4)			F[1,18]=5.8, p=.03

Results from O'Connor et al. are reported as mean (standard error); results from Malson et al. (2002, 2003) are reported at mean (±standard deviation).

*For all comparators, own brand = conventional, nonfiltered cigarettes

[a] Indicates significant difference from own brand (p<0.05, Dunnett's test).

[b] Indicates collapsed values

Table 3-6. Risk of bias, non-qualitative studies*

StudyID (first author, year published)	Aliarrah, 2009	Allen, 2003	Ashare, 2007	Blank, 2011	Blank, 2011	Cobb, 2011	Dawkins, 2013	King, 2013	Klein, 2007	Malson, 2002	Malson, 2003	Manning, 2009	O'Connor, 2007	Oliver, 2013	Pepper, 2013	Regan, 2012	Smith-Simone, 2008	Soldz, 2003	Soldz, 2005	Suffin, 2014	Vander Weg, 2005	Vander Weg, 2008	Villanti, 2013
Inclusion/ exclusion criteria	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	N/A	✔	✔	X	✔	✔	✔	✔	✔	✔
Recruitment strategy	✔	✔	?	✔	?	✔	✔	X	✔	✔	✔	✔	?	N/A	✔	✔	X	X	X	✔	✔	✔	✔
Selection of the comparison group	N/A	✔	✔	✔	✔	✔	N/A	N/A	N/A	N/A	N/A	✔	✔	✔	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Outcome assessor blinding	N/A	N/A	N/A	N/A	✔	N/A	N/A	N/A	N/A	N/A	N/A	N/A	?	N/A	N/A	N/A	N/A	N/A	N/A	✔	N/A	N/A	N/A
Valid and reliable measures	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Measures implemented consistently	X	✔	✔	✔	✔	✔	X	✔	✔	✔	✔	?	X	N/A	✔	✔	X	✔	✔	X	✔	?	✔
Length of follow-up	N/A	N/A	N/A	✔	N/A	✔	N/A	N/A	N/A	N/A	N/A	N/A	N/A	✔	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Loss to follow-up	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Primary outcomes missing	✔	✔	X	✔	✔	✔	✔	✔	✔	✔	✔	✔	?	✔	✔	✔	✔	✔	✔	✔	✔	X	✔
Results believable	?	✔	?	✔	✔	✔	?	✔	✔	?	✔	✔	X	?	?	✔	✔	✔	✔	✔	✔	✔	✔
Attempt to balance the allocation	N/A	N/A	✔	X	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Confounding variables	N/A	N/A	✔	✔	✔	✔	N/A	N/A	✔	N/A	N/A	✔	X	✔	✔	N/A	N/A	N/A	N/A	N/A	✔	N/A	N/A
Analytic techniques	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	?	✔	✔	?	✔	✔	✔	✔	✔	✔
Allocation sequence generation	N/A	N/A	?	?	?	N/A	N/A	N/A	N/A	N/A	N/A	?	?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Allocation concealment	N/A	N/A	N/A	N/A	✔	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Knowledge of the allocated intervention prevented	N/A	N/A	N/A	N/A	✔	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

*A checkmark indicates that the study was not susceptible to bias. An "X" indicates that the study was susceptible to bias. A question mark indicates that it was unclear if the study was susceptible to bias. "N/A" indicates that this question was not applicable for the study.

Table 3-7. Qualitative study results

StudyID (first author, year published)	Flavored Tobacco Products Assessed	Topic Explored	Summary of Main Result/s
Choi, 2012	E-cigarettes, Snus, Orbs, Other non-combustible products	General perceptions of new tobacco products and e-cigarettes	Participants thought the flavors of dissolvable tobacco products made them fun and interesting to use. Female participants described the pill-form dissolvable tobacco products (Camel Orbs) as “candy that gives you a little buzz” and ‘fresh and minty.’
Griffiths, 2011	Hookah/water pipe	Conditions and occasions under which participants engaged in hookah smoking, their beliefs and attitudes about hookah versus cigarette smoking, and their knowledge of risks and health outcomes of hookah smoking	The authors found that the appealing fruit-flavored sheesha disguised the true risks of hookah smoking and supported the illusion of being safer than cigarettes for participants. These factors led to the tendency among participants to rationalize away the risks of sheesha smoking and to contradict prior knowledge or general beliefs about smoking. Participants’ view that the fruit flavors contained in sheesha are similar to foods contributed to their denial of the possible presence of toxins in sheesha that may cause harm. Several participants also balked at the idea that hookah may be even remotely addictive, claiming that what is smoked is mostly herbs or flavored tobacco that does not contain the same ingredients as cigarettes.
Lavo, 2004	Chew, Spit, Other non-combustible products	Taste as an influence upon the consumption behavior of adolescents	Subjects indicated that their behavior regarding product consumption was governed by the taste of the products consumed. Subjects’ statements indicated a preference for mentholated or “minty” tasting products; they expressed preferences for Skoal Wintergreen or Skoal Mint. In relation to the consumption of smokeless tobacco, subjects reported that their preferred brand was chosen because it was sweet and did not even taste like tobacco.
Liu, 2012	Chew, Snus, Orbs, Other non-combustible products	Adult perceptions of smokeless products	Adults perceived the weak taste and candy-like flavor of novel ST products as characteristics designed to target adolescents. Adults viewed novel ST products as starter products designed to entice youth and get them addicted.
Richter, 2008	Hookah/water pipe, Kreteks/cloves	Reasons for initiating and using non-traditional tobacco products	Reasons for initiation of cloves included curiosity about the smell and taste of the products. Reasons for continuing to smoke these products included the perceived strength and convenience of these products. Participants perceived clove cigarettes as being “strong.” Smoking these products resulted in "getting more" than from a traditional cigarette. Clove cigarettes were noted to last longer than traditional cigarettes. Several participants noted that the ability to smoke non-traditional tobacco products like clove cigarettes over several sessions was seen as a convenience and a result to continue using the product. At the same time, some participants noted that non-traditional tobacco products like cloves could be harder to locate for purchase and therefore were inconvenient to use.
Sifaneck, 2005	Cigar products (cigars, little cigars, cigarillos)	Reasons for using flavored cigar-for-blunts	Blunt users reported that flavored cigar-for-blunts and blunt wraps help them conceal their consumption and possession of an illicit drug, especially in public locations.

Table 3-8. Risk of bias, qualitative studies*

StudyID (first author, year published)	Choi, 2012	Griffiths, 2011	Lavo, 2004	Liu, 2012	Richter, 2008	Sifaneck, 2005
Inclusion/exclusion criteria	✔	?	✔	✔	✔	?
Recruitment strategy	X	X	?	X	X	X
Selection of the comparison group	N/A	N/A	N/A	✔	✔	N/A
Outcome assessor blinding	N/A	N/A	N/A	N/A	N/A	N/A
Valid and reliable measures	?	?	?	?	?	?
Measures implemented consistently	✔	✔	✔	?	?	✔
Length of follow-up	N/A	N/A	N/A	N/A	N/A	N/A
Loss to follow-up	N/A	N/A	N/A	N/A	N/A	N/A
Primary outcomes missing	✔	✔	✔	✔	✔	X
Results believable	✔	✔	✔	X	?	?
Attempt to balance the allocation	N/A	N/A	N/A	✔	X	N/A
Confounding variables	N/A	N/A	N/A	N/A	N/A	N/A
Analytic techniques	✔	✔	✔	X	✔	?
Data transcribed verbatim	✔	✔	✔	✔	✔	✔
Questions predefined	✔	✔	✔	✔	✔	?
Facilitator/interviewers trained	✔	?	✔	✔	✔	?
Saturation	X	X	X	X	X	X
Research themes	✔	✔	✔	✔	✔	X
Analysis by more than one assessor	✔	?	X	✔	✔	?
Participant answers reviewed	?	?	✔	?	?	?
Sequences from data presented	✔	✔	✔	✔	✔	✔

*A checkmark indicates that the study was not susceptible to bias. An "X" indicates that the study was susceptible to bias. A question mark indicates that it was unclear if the study was susceptible to bias. "N/A" indicates that this question was not applicable for the study.

Chapter 4 - Policy Options to Regulate Flavored Tobacco Products: Development and Results of a Heuristic Model

ABSTRACT

Introduction: The goals of this study were to develop a heuristic decision tree in order to begin to model the population-level health impact of different approaches to regulating the sale of flavored tobacco products, and to organize relevant research that informs the model.

Methods: We developed a decision tree to compare three policy options: 1) the banning of all flavored combustible tobacco products, 2) the banning of all flavored tobacco products (inclusive of combustible and smokeless products), and 3) the status quo, in which only flavored cigarettes are banned. The model examines outcomes for a cohort of healthy 18-year-old never tobacco users. The timeframe for the model is 15 years and the analytic horizon spans the lifetime. The model estimates health effects, expressed on a unitless scale. We conducted univariate and multivariate sensitivity analyses to assess uncertainty in the model.

Results: The results of this heuristic model found that a ban on all flavored tobacco products would likely produce the most favorable outcome of the policy options considered. The parameters that contributed to the majority of the uncertainty in the model were: 1) the probability of combustible tobacco initiation under the status quo, 2) the probability of smokeless tobacco initiation under the status quo, and 3) the health effect associated with dual (combustible/smokeless) tobacco use. In the multivariate

analysis, the preferred decision option changed for 13.3% of combinations of values tested.

Conclusions: This model provides a framework for examining regulatory approaches intended to reduce the attractiveness of tobacco products. It weighs the impact of reducing the attractiveness of some products but not others, while taking into consideration the varying levels of risk that different products present. This analysis serves as a first step to developing more complex model; future studies should update this model as relevant evidence is published.

INTRODUCTION

Under the Family Smoking Prevention and Tobacco Control Act (FSPTCA) of 2009, cigarettes with characterizing flavors, excluding menthol, were banned in the United States (1). This ban did not apply to non-cigarette tobacco products. However, in April 2014, the U.S. Food and Drug Administration (FDA) published a proposed ruling in which it requested research and data to support the extension of the flavored cigarette ban to other tobacco products (2).

As part of the FSPTCA, the FDA is mandated to issue tobacco regulations "appropriate for the protection of the public health" (1). In contrast to the individual-level "safe and effective" standard that FDA-regulated products are traditionally required to meet, this public health standard allows the FDA to consider the population-level effects of tobacco products when enacting regulatory decisions (3). Specifically, the FDA is to consider the effect that a tobacco product will likely have on 1) initiation of tobacco product use

among non-users, 2) cessation of tobacco product use among users, and 3) overall risks and benefits to the entire population (1).

"Traditional" scientific evidence, such as data from randomized controlled trials (RCTs), is rarely sufficient to directly inform these criteria. There are often limits to the generalizability of RCTs, and the outcomes in which we are interested—such as health effects—are often not measureable in the short-term, particularly when examining the effect of a tobacco control policy or intervention on a young population (4, 5). To assess tobacco control policies in a timeframe that is short enough to inform imminent regulatory decisions, the FDA has shown an interest employing evidence from mathematical modeling studies (6, 7).

The goals of this study were to develop a heuristic decision tree, a type of mathematical model, in order to begin to model the population-level health impact of different approaches to regulating the sale of flavored tobacco products, and to organize the relevant research that informs the model. This model compares three policy options, and while the output identifies a preferred regulatory approach among the three options, it is not intended to be predictive model. Rather, this is a heuristic model that employs the best available evidence to inform a policy decision that may need to be made within a short timeframe. As a heuristic tool, this model is intended to present a preliminary framework that can be used to consider the effects of tobacco control policies, organize relevant data, and determine which parameters have the greatest influence on population-level health (8). We chose the following policy options to represent alternative

conceptual approaches to reducing the harm caused by tobacco use:

- The banning of all flavored combustible tobacco products
- The banning of all flavored tobacco products (inclusive of combustible and smokeless products)
- The status quo, in which only flavored cigarettes are banned

We chose the banning of all flavored combustible tobacco products to exemplify a harm reduction approach to tobacco control. While smokeless tobacco use presents unique harms when compared to combustible tobacco use, if it is used instead of combustible tobacco, the risk of experiencing negative health effects is reduced (9). By banning flavored combustible products but not flavored smokeless products, smokeless tobacco is made more attractive to tobacco users who enjoy flavored products. Thus, this approach aims to promote smokeless tobacco as an alternative to combustible tobacco.

There are many types of policies aimed at reducing the negative effects of tobacco use that could be characterized as harm reduction policies. For example, proponents of a harm reduction approach often point to Sweden for a successful example of this strategy; in Sweden, an increase in prevalence of the smokeless tobacco product "snus" corresponded with a decline in smoking prevalence (10, 11). While the banning of all flavored combustible tobacco products was chosen to exemplify a harm reduction approach to tobacco control in the context of this paper, it should be noted that this policy option is not the only available strategy that could represent a harm reduction approach.

Opponents of harm reduction strategies often emphasize the negative unintended consequences that such policies may produce. The banning of all flavored combustible products may have unintended consequences, as it is successful only if users who engage in combustible tobacco use substitute their use of combustible products with smokeless products. If these combustible users initiate smokeless tobacco without reducing combustible use – or, if the uptake of smokeless tobacco causes these individuals to delay smoking cessation – then the promotion of smokeless tobacco products may actually cause more, rather than less, harm when compared to a ban on all flavored products or the status quo.

We chose to examine the effects of a ban on all flavored tobacco products in this model, because this policy takes the potential unintended consequences of a harm reduction approach into consideration and acknowledges that all tobacco use poses health risks. Thus, a ban on all flavored tobacco products represents a differing conceptual approach to tobacco control, in which all tobacco products, regardless of their relative harm to one another, are discouraged.

In this analysis, a ban on all flavored combustible tobacco products and a ban on all flavored tobacco products are compared with the status quo, a scenario in which the 2009 ban on flavored cigarettes exists, but no additional flavored tobacco bans are enacted. In this paper, the status quo scenario is referred to as the "no ban" scenario.

METHODS

As a conceptual underpinning, this model assumes that flavoring in tobacco products is an attractive trait that increases consumer use of tobacco (12). In this paper, "flavored" should be understood to exclude menthol, as menthol cigarettes were not included in the 2009 ban on flavored cigarettes. We used TreeAgePro 2014 to conduct this analysis.

Model Framework

The decision tree is illustrated in **Figure 4-1**. This model focuses on a young adult population, defined as 18-34 year olds. According to the U.S. Census Bureau, 18-34 year olds make up approximately 23% of the U.S. population (13), and approximately 23% (95% CI: 21-25) of 18-34 year-olds use some form of tobacco product (14). Research has shown that tobacco use behaviors are initiated and solidified during young adulthood (15-17), and analyses of tobacco industry documents have revealed that flavored tobacco products are specifically targeted towards young populations (18-20). Thus, the decision tree examines outcomes for cohort of healthy 18-year-old never tobacco users.

The timeframe for the model is fifteen years. Policies are implemented at time point zero (T_0), and all tobacco-related behavioral changes are assumed to occur between T_0 and T_{15}. We chose this timeframe because adults who quit smoking before the age of 35 are thought to avoid most of the negative health effects associated with cigarette use (21). Thus, 15 years represents a time frame after which a differential health effect will be seen among individuals with varying tobacco-related behavioral outcomes. The behavioral changes that occur between T_0 and T_{15} are assumed to "freeze" at T_{15} and persist until

death; this model assumes a lifetime analytic horizon.

Between T_0 and T_{15}, subjects undergo two major behavioral transitions, highlighted in **Figure 4-1**:

- First behavioral transition: During the first transition, individuals initiate combustible tobacco use, initiate smokeless tobacco use, or never initiate tobacco use. While some literature has considered "dual initiators" (22, 23) – individuals who begin using two tobacco products within the same year – this model assumes that product initiation must occur sequentially.
- Second behavioral transition: During the second transition, individuals who initiate tobacco use proceed to 1) continue use of the type of product (combustible or smokeless) with which they initiated ("persist"), 2) initiate use of a second type of product (combustible or smokeless) without stopping use of the product with which they initiated ("dual use"), 3) initiate use of a second type of product (combustible or smokeless) while stopping use of the product with which they initiated ("switch"), or 4) cease using tobacco altogether ("quit").

This simplified approach to representing tobacco use patterns over time reflects the depth of the data available to inform this model; insufficient data were available to inform a more complex Markov model.

In this model, combustible tobacco products include all cigar products (including cigarillos and little cigars), bidis, kreteks, hookah/shisha and pipes. Because flavored cigarettes have already been banned in the United States, they were excluded from this

model. When data differentiated between cigarette use and other combustible tobacco use, we chose data describing other combustible tobacco use to inform the model. However, when only cigarette-specific data were available, we employed these data. Smokeless tobacco products include snuff, snus, spit, chew, and dissolvable tobacco products. E-cigarettes were excluded from this model because the usage patterns and health effects of e-cigarettes are not yet well understood.

Outcomes

This model estimates health effects, expressed on a unitless scale, in which higher numerical values represent worse health outcomes. This approach was developed by Mejia et al. to assess the effects of promoting smokeless tobacco as a harm reduction strategy in the United States (24). Mejia et al. established a scale based on a panel of nine experts who were asked to assess the relative risk of mortality for users of a low-nitrosamine smokeless tobacco product compared to cigarette smokers (9). The panel perceived the low-nitrosamine smokeless tobacco product to present at least a 90% reduction in relative risk. On the health effects scale, Mejia et al. intentionally ranked dual use of cigarettes and smokeless tobacco as less harmful than current cigarette smoking under the assumption that, if smokeless tobacco were promoted for harm reduction, dual users would reduce the number of cigarettes consumed upon uptake of smokeless tobacco.

The outcomes in this model possess the same utility values employed by Mejia et al., excluding the value assigned to dual use. The model presented in this paper reflects

uncertainty with regard to whether dual use is likely to present reduced, equal, or increased harm when compared with combustible tobacco use (25). We established parameter values for dual use that reflect this uncertainty in consultation with a biostatistician to ensure that the distribution of the parameter values would, mathematically, operate properly within the model. The utility values employed in the model are presented in **Table 4-1**. For the sensitivity analysis, we assigned dual use a utility value that is greater than 100 – as opposed to maintaining a scale with a maximum value of 100 – because the panel of experts who provided data to inform Mejia et al.'s scale were told that a risk greater than that presented by cigarette use-only should be ranked higher than 100 (9). The 5th and 95th percentile values were used as minimum and maximum values in the analysis. In mathematical models, discounting is sometimes used to emphasize the present value costs and benefits over future costs and benefits (26). Conceptually, the outcomes on the health effects scale are already discounted.

Table 4-1. Tobacco-related behavioral outcomes and their utility values

	Mean	Minimum Value	Maximum Value
Combustible use only	100	-	-
Never use	0	-	-
Former use	5	1	15
Smokeless use only	11	5	20
Dual use	100	87	110

Probability Estimates

We explain the rationale for selecting the parameter values used in the below. When available, we used relevant data to produce best-guess estimates for the parameters. In cases where relevant data were unavailable, the authors' assumptions (clearly stated) informed the parameter values.

Status quo

There are no existing longitudinal studies conducted with a young adult population to inform the probability estimates in this model. Thus, we consulted other types of data to obtain reasonable probability estimates for the status quo scenario. When initiation estimates were not available, we used prevalence data in their place. Mendez, Warner and Courant (1998) have used this approach for modeling initiation in a cohort of 18 year olds (27); this approach was evaluated six years after the model was first employed, and observed data were found to fit the original model's projections closely (28). Probability estimates for the status quo scenario, along with their rationales, can be found in **Table 4-2**.

No data were available to directly inform parameter estimates for the two other policy scenarios under consideration. Thus, the status quo parameter estimates served as a reference point for estimating the remaining probability values. In estimating these values, we considered the underlying assumption that flavoring in tobacco is an attractive trait that drives initiation and persistence of tobacco use. Calculations for these values are discussed below. **Table 4-3** contains a summary of all parameter definitions.

Ban on all flavored tobacco products

We assume that a ban on all flavored tobacco products impacts only individuals who would have initiated tobacco use with a flavored product under the status quo. Villanti et al. found that, among 18-34 year olds, 29.8% of current combustible tobacco users used a flavored combustible tobacco product in the past 30 days, and 8.2% of current smokeless

tobacco users used a flavored smokeless tobacco product in the past 30 days (29). For the present model, we employed these values as flavored tobacco initiation rates. In a previous study, Levy et al. modeled the effects of a menthol cigarette ban in the United States (30). The authors of this study examined three scenarios, in which menthol cigarette initiation rates were reduced by 10%, 20% and 30% after the implementation of the ban. We applied these values in the present model. As a baseline value, we assumed that 20% of individuals who would have initiated tobacco use with a flavored product under the status quo do not initiate tobacco use at all. We assumed the remaining 80% of these individuals initiate tobacco use with a nonflavored version of the product with which they would have otherwise initiated under the status quo. For the pessimistic and optimistic scenarios, we assumed 10% and 30% reductions in initiation, respectively. Values for the parameters representing the second behavioral transition in the model – in which tobacco initiators can switch products, become dual users, quit tobacco, or continue use of the product with which they initiated - are identical to their corresponding probabilities under the status quo.

Ban on combustible flavored tobacco products

The model assumes that a ban on flavored combustible products impacts only those who would have used a flavored combustible product under the status quo. The parameter values for combustible tobacco initiation under this scenario are identical to those estimated for combustible tobacco initiation under a ban on all flavored tobacco products. However, because flavored smokeless tobacco is still available in this scenario, we assumed that some individuals who do not initiate combustible tobacco due to the ban

instead initiate smokeless tobacco use. This supposition is consistent with an analysis in which researchers examined cigarillo use trends among Canadian youth following a ban on flavored cigarillos (31). The results of this study showed that there was a reduction in the overall use of cigarillos after the ban, and that there was a small increase in the use of regular cigars, which were still permitted to be flavored. The authors suggested that the flavor ban produced a net decrease in cigar use, but that the increase in regular cigar use may have been an unintended consequence of the ban. Thus, as a baseline value for the first behavioral transition in the present model, half of the individuals who did not initiate combustible tobacco use due to the ban on flavored combustible tobacco products instead initiate smokeless tobacco use; the other half never initiate tobacco use. The low value for this parameter models a scenario in which all of the individuals who did not initiate combustible tobacco use due to the ban never initiate tobacco, and the high value models a scenario in which all of those individuals instead initiate smokeless tobacco use.

For the second behavioral transition, because flavored smokeless tobacco products are available under this scenario, switching rates from combustible to smokeless products, as well as rates of dual use among combustible initiators, are higher than they are under the status quo. The model assumes that a 3% increase in the rates of switching to smokeless products and transitioning to dual use occurs compared to the status quo. The minimum and maximum values model 1% and 6% increases, respectively. The probability of quitting tobacco among combustible tobacco initiators remains constant when compared to the status quo. Among smokeless tobacco initiators, rates of switching to combustible tobacco and rates of dual use are lower than they are under the status quo. The model

assumes that a 3% decrease in switching rates to combustible products and transitioning to dual use occurs when compared to the status quo. The minimum and maximum values model 6% and 1% decreases, respectively. The probability of quitting tobacco among smokeless tobacco initiators remains constant when compared to the status quo.

The estimates for the first and second behavioral transitions are not directly informed by data; they are intended to be conservative values.

Analysis

We used TreeAgePro 2014 to calculate the expected utility for each policy option. To calculate the expected utility, TreeAgePro multiplies the value of each outcome for each branch by its estimated probability, and sums the products of those calculations for each branch of the tree. Lower expected utilities represent favorable (less harmful) outcomes in this analysis. We performed sensitivity analyses to assess the robustness of the expected utility calculations and to determine how the results of the decision tree changes given uncertainty in the data. We conducted univariate analyses on all variables with uncertain parameter values to identify the variables that drive the model and ensure that the model was operating as expected. Variables having the most impact on the model were investigated further in multivariate analyses.

RESULTS

The output of this heuristic model found that, under the baseline scenario, the expected utility for the status quo was 18.91. This value was higher (representing increased harm)

when compared to the ban on combustible flavored tobacco products, which produced a utility value of 18.42, as well as the ban on all flavored tobacco products, which produced a utility value of 17.97. These relative rankings can be understood with regard to the unitless scale upon which the model's outcome was based; a cohort of 100% combustible-only tobacco users would have produced an expected utility of 100, and a cohort of 100% never tobacco users would have produced an expected utility of 0.

We conducted univariate sensitivity analyses and generated a tornado diagram. The analysis included all variables for which there was uncertainty. **Figure 4-2** illustrates the main results of the analysis, and **Appendix 4-1** contains detailed results. In **Figure 4-2**, the longest bars, located at the top of the diagram, represent variables that have the greatest impact on the model output. The hashed vertical line represents the expected utility value for the status quo. Bar extensions to the left of the hashed vertical line represent values lower than the expected utility value, and bar extensions to the right of the hashed vertical line represent values higher than the expected utility value. We identified nine variables that contributed to uncertainty in the expected values generated by the model, listed in **Table 4-4**. Three variables contributed 83% of the uncertainty in the model; these variables represented 1) the probability of combustible tobacco initiation under the status quo, 2) the probability of smokeless tobacco initiation under the status quo, and 3) the health effect associated with dual (combustible/smokeless) tobacco use.

It is reasonable that these three variables were found to be the most impactful, which suggests that the model operated as expected. The first transition in the model, in which tobacco initiation occurs, is the major determinant of the terminal outcome. That is, there

is substantially less switching between branches during the second behavioral transition, as opposed to the first. Of the first transitions, the probability of combustible tobacco initiation and the probability of smokeless tobacco initiation under the status quo have the widest high/low ranges; this occurred by design, as we used the tobacco initiation rates from the status quo scenario to inform the tobacco initiation rates for the ban on all flavored tobacco products and the ban on combustible flavored tobacco products based on those for the status quo. Thus, the uncertainty about the first transition values under the status quo should be understood to reflect uncertainty about the first transition probabilities under the other scenarios. With regard to the uncertainty around the health effect associated with dual (combustible/smokeless) tobacco use – this parameter was specifically intended to be uncertain and impactful upon model results. These results indicate that the model operated at expected.

To address 83% of the uncertainty in the model, we further investigated the probability of combustible tobacco initiation under the status quo, the probability of smokeless tobacco initiation under the status quo, and the health effect associated with dual (combustible/smokeless) tobacco use. For the multivariate analyses, we conducted three two-way analyses, where each variable under consideration was analyzed along with each of the other two variables of interest. **Appendix 4-2** contains the complete results of these analyses.

In the analysis that varied the probability of combustible tobacco initiation under the status quo and the probability of smokeless tobacco initiation under the status quo, the

most favorable expected value was 16.53 and the least favorable expected value was 21.58. We examined seventy-five combinations of values for the two parameters. For 8% of the combinations, the expected utility values changed such that the most favorable policy option was the status quo, as opposed to a ban on all flavored tobacco products. The expected utility values can be found in **Appendix 4-2**. This finding reinforces the importance of obtaining valid data to inform the initial transition probabilities.

When we varied the health effect of dual use with the initial transition probabilities, 13.3% of the combinations of values changed the preferred policy option such that a ban on combustible products would be favored, and 2.7% of the combinations of values changed the preferred decision such that the status quo would be favored. The changes in the preferred decision option do not occur when the health effect of dual use is only modeled to be slightly more or less harmful than combustible tobacco use-only; they occur at the extreme values assigned to the health effect outcome for dual use. In order to bolster confidence in the results, it is necessary to conduct research to determine whether dual users of combustible and smokeless products are likely to be exposed to more or less harm than combustible-only users, and to what extent.

Table 4-4. Variables that contribute to model uncertainty, listed in descending order of importance

Variable	Risk Percent*	Cumulative Risk Percent*
Probability of combustible tobacco use - status quo	0.46717182	0.46717182
Probability of ST initiation - status quo	0.220366608	0.687538428
Health effect from dual use	0.147320554	0.834858982
Probability of switching to ST use among combustible initiators - status quo	0.053534168	0.88839315
Probability of quitting tobacco use among combustible initiators - status quo	0.050409557	0.938802708
Health effect from ST use	0.038872179	0.977674886
Probability of quitting tobacco use among ST initiators - status quo	0.01597113	0.993646016
Health effect from former tobacco use	0.003301299	0.996947315
Probability of continuing to use ST among ST initiators - status quo	0.003052685	1

*The Risk Percent measures the total uncertainty represented by the variable. The Cumulative Risk Percent is a cumulative version of the Risk Percent.

DISCUSSION

The results of this analysis found that, given the structural and parameter assumptions upon which this model was built, a ban on all flavored tobacco products would likely produce the most favorable outcome when compared to a ban on combustible flavored products or the status quo. In the base case scenario, the expected utilities for the status quo, ban on combustible flavored tobacco products, and ban on all flavored tobacco products were 18.91, 18.42 and 17.97, respectively. The scale from which these values were derived represented informed best guesses by experts about the relative harm associated with tobacco use behaviors included in this model. While the difference between the highest and lowest expected utilities (0.94) was small, when applied to the model's large hypothetical cohort of young adults in the United States, a small improvement in the outcome value represents health benefits to a substantial number of individuals.

In the sensitivity analysis, three parameters were found to account for 83% of the uncertainty in the model: 1) the probability of combustible tobacco initiation under the status quo, 2) the probability of smokeless tobacco initiation under the status quo, and 3) the health effect associated with dual (combustible/smokeless) tobacco use. In the

multivariate analysis, the rankings of the decision options changed for 13.3% of combinations of values tested across the three two-way analyses. These findings suggest that implementing at least one of the bans is likely to produce a favorable health effect at the population level; however, there is a small chance that implementing a ban could cause a negative health effect.

Assumptions about parameter values contributed to uncertainty in the results, and research should be conducted to address this uncertainty for future iterations of the model. The Methods section, and specifically **Table 4-2**, provides an overview of the data that were available to inform the parameters in this model. This overview highlights the lack of directly relevant, generalizable data to inform this model. For example, prevalence data were used to inform parameters representing initiation in this model. Future studies should collect product- and flavor-specific data that explicitly investigates tobacco experimentation and initiation behaviors, as well as longitudinal data to track use over time. In general, the lack of data available to inform directly the parameter estimates emphasizes the need to monitor polytobacco use patterns in order to gain a better understanding of the types of products with which non-users initiate tobacco use, and the extent to which adding or removing certain products from the marketplace is likely to increase or decrease exposure to harm.

Structural assumptions also contributed to uncertainty in the results of this analysis. This model presents a simplified version of the environment in which tobacco use occurs and the factors impacting tobacco use in a number of ways. For example, representing

tobacco use behaviors with only two opportunities for individuals in the model transition behaviors – as well as assuming that tobacco use behaviors are unchanged after T_{15} – does not reflect actual tobacco use patterns. Conceptually, a Markov model may better represent tobacco use behaviors over time. However, data were not available to support the development of a Markov model. As better data become available, the decision tree that we present in this paper can be used as a framework to inform a model that reflects more complex behavior changes over time.

Given the limited availability of data to inform the model, we aimed to be conservative in estimating the effects of the policies under consideration. That is, the estimated impact of the two product bans would likely be greater than the results of this model indicate. First, by focusing on a young adult cohort, we did not assess the impact of the policies for other age groups. We chose the young adult cohort because this group is likely to experience the greatest impact from a ban on flavored tobacco products. However, if the FDA were to implement either of the bans considered in this model, other age groups would likely experience effects, as well. Thus, the impact of the bans would likely be greater than this model suggests. Second, this model did not examine the effects of the policies on individuals who initiated tobacco use prior to T_0. It is likely that individuals already using flavored tobacco products– particularly those using flavored products exclusively – might quit tobacco or reduce their tobacco use if their flavored product of choice were banned.

This model was also, perhaps, conservative in its assumptions about the health effects of dual use, which contributes to the finding that a ban on all flavored products is likely

preferred to a ban on combustible flavored products. For the health effect of dual use, we assigned a range of utility values representing a possible 13% decrease or 10% increase in harm when compared to combustible-only users. We chose these values to capture uncertainty with regard to whether dual users are more or less likely to be exposed to harm than combustible-only users. In the sensitivity analysis, when we employed the lower value for the health effect of dual use (representing a 13% decrease in harm) alongside varied values for the initial transition probabilities, a ban on combustible flavored products was sometimes preferred over a ban on all flavored products. This is notable because the outcome values in this model do not take intensity or frequency of tobacco use into consideration. In actuality, if a dual user significantly reduces combustible use, the reduction in harm when compared to combustible-only use could be much more significant than the values in the current model reflect. Thus, a model that incorporates changes in intensity and frequency of tobacco use may find that a harm reduction approach is a preferred over a ban on all flavored combustible products.

This model provides a framework for examining regulatory approaches intended to reduce the attractiveness of tobacco products. It weighs the impact of reducing the attractiveness of some products but not others, while taking into consideration the varying levels of risk that those different products present. This model could be adjusted to address a range of policy issues. For example, in the proposed ruling published in April 2014, the FDA asks, “Does one's use of fruit and candy-flavored nicotine liquids impact the likelihood that such individual will initiate use of combustible tobacco products and/or become a dual user with combustible tobacco products? How should that

affect FDA's regulatory decisions regarding e-cigarettes (2)?" The model presented in this paper could be built upon to address this question directly.

CONCLUSION

This heuristic model synthesizes the best available evidence to provide decision-makers with data on potential approaches to regulating the sale of flavored tobacco products. While this model was limited by the research available to inform its parameter values, it provides a framework for examining regulatory approaches intended to reduce the attractiveness of tobacco products. It weighs the impact of reducing the attractiveness of some products but not others, while taking into consideration the varying levels of risk that different products present. Thus, as additional data is collected, this model can be updated. Models such as this one may serve as an important resource for policymakers at the FDA.

Table 4-2. Probability estimates – status quo scenario

Pathway	Definition	Base Case Estimate (Range)	Rationale and Citations
Combustible initiation	Probability of initiating combustible tobacco use	0.167 (0.148-0.187)	The 2013 Youth Risk Behavior Survey estimated that 16.7% (95% CI: 14.8-18.7) of 12th grade students smoked a cigar in the past 30 days (32).
Combustible persistence	Probability of persistence of combustible tobacco use-only among combustible initiators	0.695 (0.532-0.8415)	The 2012 National Adult Tobacco Survey estimated that, among adults aged 18+ using tobacco, 92.08% use combustible products only (33). This figure includes those who initiated with smokeless products but no longer use them, as well as data for older adults; thus, this estimate may be high. A longitudinal study conducted in Oregon in which 7th and 9th grade boys were followed over two years between 1994 and 1999 found that, of individuals who used cigarettes at the first time point, 47% used cigarettes and not smokeless tobacco at the second time point (34). Given the brief follow up period and the potentially dated nature of the data, this estimate may be low. An average of these two estimates was calculated in order to obtain the base case value for this parameter. The lower and upper parameter values were estimated based on the upper and lower values for the other parameters.
Dual use	Probability of dual use (combustible + smokeless) among combustible initiators	0.132 (0.025-0.24)	The 2012 National Adult Tobacco Survey estimated that, among adults aged 18+ using tobacco, 2.448% use combustible products only (33). This figure includes those who initiated with smokeless products but no longer use them. A longitudinal study conducted in Oregon in which 7th and 9th grade boys were followed over two years between 1994 and 1999 found that, of individuals who used cigarettes at the first time point, 24% were using both combustible and smokeless tobacco (34). An average of these two estimates was calculated in order to obtain the base case value for this parameter.
Switching	Probability of smokeless tobacco use-only (switching) among combustible initiators	0.033 (0.0165-0.066)	The estimate for the base case value was obtained by subtracting the sum of the other parameters from 1. The upper and lower parameter values were estimated to be twice as large at the base case value, and half as large as the base case value, respectively.
Quitting	Probability of quitting all combustible and smokeless tobacco products among combustible initiators	0.14 (0.117-0.162)	Among 16-17 year olds who initiated tobacco use with cigarettes (as opposed to initiating with smokeless tobacco or with cigarettes and smokeless tobacco at the same time), 48.6% (95% CI: 46.3-50.9) smoked at least 100 cigarettes in their lifetime, and 42.8 (95% CI: 40.5-45.2) were current cigarette smokers (past 30 days) (22). Therefore, we assume that, among those who initiate tobacco use with cigarettes, smoking "doesn't stick" at this age for 5.8% of the sample (math: 48.6%-41.8% = 5.8%). This number may be high, as 16-17 year olds still may develop regular cigarette smoking habits as older adolescents and young adults. It has also been estimated that 8.2% (95% CI: 5.9-10.5) of 18-24 year olds recently achieved smoking cessation (35); this was among current smokers who smoked for at least 2 years and former smokers who quit in the past year. Among individuals who initiate with combustible tobacco use, and taking into consideration both individuals who develop regular smoking habits and those who do not, we assume that 14% will quit tobacco use by age 24 (math: 5.8% + 8.2% = 14%). The

Table 4-2. Probability estimates – status quo scenario

			lower and higher values of the confidence intervals for these estimates were used to obtain the lower and higher parameter values in a similar fashion.
Smokeless initiation	Probability of initiating smokeless tobacco use	0.094 (0.079-0.113)	The 2013 Youth Risk Behavior Survey estimated that 9.4% (95% CI: 7.9-11.3) of 12th graders had used smokeless tobacco in the past 30 days (32).
Smokeless persistence	Probability of persistence of smokeless tobacco-only among smokeless initiators	0.386 (0.376-0.397)	The 2003, 2005 and 2007 National Surveys on Drug Use and Health found that, among adults age 18+ who initiated with smokeless tobacco, 48.8% (95% CI: 46.7-50.8) had smoked at least 100 cigarettes in their lifetime (22). We assume, then, that 51.2% (math: 100%-48.8%) of smokeless tobacco initiators never "make it" to dual use. A longitudinal study conducted in Oregon in which 7th and 9th grade boys were followed over two years between 1994 and 1999 found that, of individuals who used smokeless tobacco at the first time point, 26% reported continuing with smokeless tobacco use only at follow up (34). An average of these two values was calculated to obtain the base case value for this parameter. The lower and higher values of the confidence interval for the NSDUH estimate were averaged with 26% to obtain the lower and higher parameter values.
Dual use	Probability of dual use (combustible + smoking) among smokeless initiators	0.33 (0.153-0.435)	The 2003, 2005 and 2007 National Surveys on Drug Use and Health found that, among 16-17 year olds who initiated with smokeless tobacco, 18.4% (95% CI: 14.4-23.0) were current cigarette smokers (22). This includes both dual users and those who switched to cigarettes, so this would be a high estimate of dual use. At the same time, this figure only includes 16-17 year olds; some individuals will develop dual use habits as older adolescents and young adults. Among adults aged 18+ in the same sample, 27.9% (95% CI: 25.9-30.0) of those who initiated with smokeless tobacco were current cigarette smokers (22). A longitudinal study conducted in Oregon in which 7th and 9th grade boys were followed over two years between 1994 and 1999 found that, of individuals who used smokeless tobacco at the first time point, 40% reported dual use at follow up (34). Additionally, one study looking at middle and high school students found that 60.2% (95% CI: 50.0-69.6) of current smokeless tobacco users were also current cigarette users (23). Taking all of these estimates into consideration, We assume that 33% of those who initiate with smokeless tobacco will become dual users as a base case estimate. The lower and upper parameter values were estimated based on the upper and lower values for the other parameters.
Switching	Probability of combustible tobacco use-only (switching) among smokeless initiators	0.144 (0.072-0.288)	The estimate for the base case value was obtained by subtracting the sum of the other parameters from 1. The upper and lower parameter values were estimated to be twice as large at the base case value, and half as large as the base case value, respectively.
Quitting	Probability of quitting all combustible and smokeless tobacco products among smokeless initiators	0.14 (0.117-0.162)	It is unknown whether individuals who initiate with smokeless tobacco are more or less likely than those who initiate with combustible tobacco to quit tobacco by age 24. Therefore, we assume the probability of quitting tobacco altogether is the same between these two groups.

Table 4-2. Probability estimates – status quo scenario

Never initiation	Probability of never initiating tobacco use	0.739 (0.70-0.773)	This estimation was obtained by subtracting the number of combustible and smokeless initiators from the total sample. This number is close to the number of high school students who were estimated never to have tried any tobacco product in 2012 (76.7%) (35), so it is likely a good estimate. The lower and upper parameter values were estimated based on the upper and lower values for the other parameters.

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Table 4-3. Variable names, descriptions and values

Variable	Baseline Value	Low Value	High Value
Health effect from combustible tobacco use	100	100	100
Health effect from dual (combustible/smokeless) tobacco use	100	87	110
Health effect from never tobacco use	0	0	0
Health effect from former tobacco use	5	0	5
Health effect from smokeless tobacco use	11	5	20
Probability of initiating combustible use - ban on all flavored tobacco products	0.157	0.152	0.162
Probability of ST initiation - ban of all flavored tobacco products	0.092	0.092	0.093
Probability of initiating combustible tobacco use - ban on flavored combustible tobacco products	0.157	0.152	0.162
Probability of dual use among combustible initiators – ban on combustible flavored products	0.136	0.133	0.14
Probability of quitting tobacco among combustible initiators - ban on combustible flavored products	0.14	0.117	0.162
Probability of smokeless tobacco use among combustible initiators - ban on combustible flavored products	0.034	0.033	0.035
Probability of initiating with smokeless tobacco - ban on combustible flavored products	0.099	0.094	0.104
Probability of combustible use among ST initiators - ban on combustible flavored products	0.140	0.135	0.143
Probability of quitting tobacco among ST initiators - ban on combustible flavored products	0.14	0.117	0.162
Probability of continuing ST use among ST initiators - ban on combustible flavored products	0.374	0.363	0.382
Probability of combustible tobacco use - status quo	0.167	0.148	0.187
Probability of dual use among combustible initiators - status quo and ban on all flavored tobacco products	0.132	0.025	0.24
Probability of quitting tobacco use among combustible initiators - status quo and ban on all flavored tobacco products	0.14	0.117	0.162
Probability of switching to ST use among combustible initiators - status quo and ban on all flavored tobacco products	0.033	0.0165	0.066
Probability of ST initiation – status quo	0.094	0.079	0.113
Probability of switching to combustible use among ST users - status quo and ban on all flavored tobacco products	0.144	0.072	0.288
Probability of quitting tobacco use among ST initiators - status quo and ban on all flavored tobacco products	0.14	0.117	0.162
Probability of continuing to use ST among ST initiators - status quo and ban on all flavored tobacco products	0.386	0.376	0.397

Figure 4-1. Decision tree framework

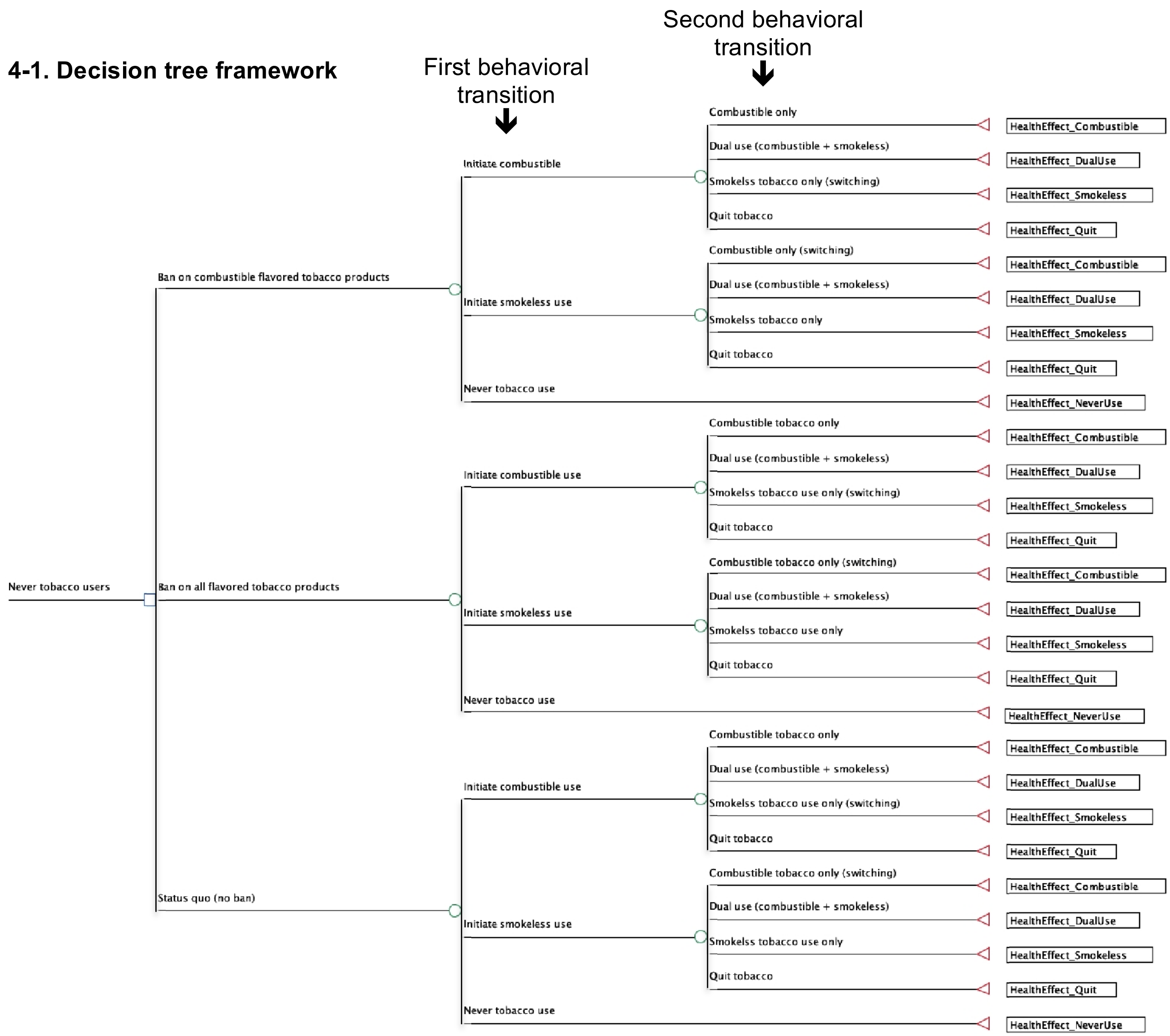
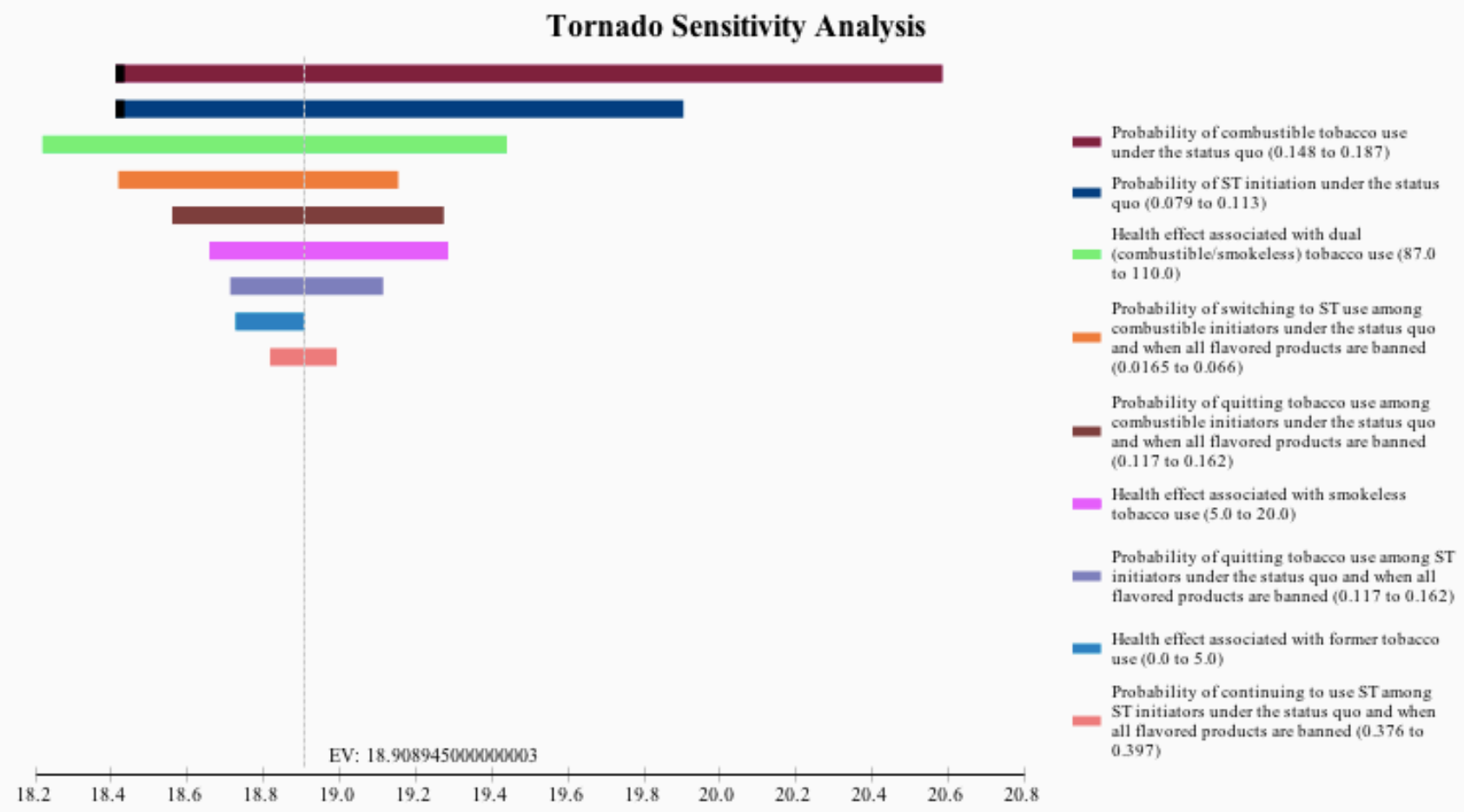


Figure 4-2. Tornado sensitivity analysis



Appendix 4-1. Results from the univariate sensitivity analysis - TreeAgePro output

Variable	VARIABLE RANGE	LOW VALUE	HIGH VALUE	SPREAD	SPREAD SQR	RISK PCT	CUMUL PCT	VARIABLE INDEX
Probability of combustible tobacco use under the status quo	0.148 to 0.187	18.410831	20.584205	2.173374	4.723554544	0.46717182	0.46717182	0
Probability of ST initiation under the status quo	0.079 to 0.113	18.410831	19.903519	1.492688	2.228117465	0.220366608	0.687538428	1
Health effect associated with dual (combustible/smokeless) tobacco use	87.0 to 110.0	18.219113	19.439585	1.220472	1.489551903	0.147320554	0.834858982	2
Probability of switching to ST use among combustible initiators under the status quo and when all flavored products are banned	0.0165 to 0.066	18.418466	19.1541845	0.7357185	0.541281711	0.053534168	0.88839315	3
Probability of quitting tobacco use among combustible initiators under the status quo and when all flavored products are banned	0.117 to 0.162	18.559915	19.27384	0.713925	0.509688906	0.050409557	0.938802708	4
Health effect associated with smokeless tobacco use	5.0 to 20.0	18.658175	19.2851	0.626925	0.393034956	0.038872179	0.977674886	5
Probability of quitting tobacco use among ST initiators under the status quo and when all flavored products are banned	0.117 to 0.162	18.712485	19.114335	0.40185	0.161483423	0.01597113	0.993646016	6
Health effect associated with former tobacco use	0.0 to 5.0	18.726245	18.908945	0.1827	0.03337929	0.003301299	0.996947315	7
Probability of continuing to use ST among ST initiators under the status quo and when all flavored products are banned	0.376 to 0.397	18.816919	18.992605	0.175686	0.030865571	0.003052685	1	8
Probability of dual use among combustible initiators under the status quo and when all flavored products are banned	0.025 to 0.24	18.908945	18.908945	3.55271E-15	1.26218E-29	1.24833E-30	1	9
Probability of quitting tobacco among ST initiators under a ban on flavored combustible tobacco products	0.117 to 0.162	18.908945	18.908945	0	0	0	1	10
Probability of continuing ST use among ST initiators under a ban of flavored combustible tobacco products	0.363 to 0.382	18.908945	18.908945	0	0	0	1	11
Probability of ST initiation under a ban of all flavored tobacco products	0.092 to 0.093	18.908945	18.908945	0	0	0	1	12
Probability of initiating combustible use under a ban on all flavored tobacco products	0.152 to 0.162	18.908945	18.908945	0	0	0	1	13
Probability of switching to combustible use	0.072 to 0.288	18.908945	18.908945	0	0	0	1	14

among ST users under the status quo and when all flavored products are banned								
Probability of combustible use among ST initiators, given flavored combustible ban	0.135 to 0.143	18.908945	18.908945	0	0	0	1	15
Probability of dual use among combustible initiators, given a flavored combustible ban	0.133 to 0.14	18.908945	18.908945	0	0	0	1	16
Probability of quitting tobacco among those who initiated with combustible tobacco, under a flavored combustible ban	0.117 to 0.162	18.908945	18.908945	0	0	0	1	17
Probability of initiating with smokeless tobacco, given a flavored combustible ban	0.094 to 0.104	18.908945	18.908945	0	0	0	1	18
Probability of initiating combustible tobacco use, given a ban on flavored combustible tobacco products	0.152 to 0.162	18.908945	18.908945	0	0	0	1	19

Appendix 4-2. Results from the multivariate sensitivity analysis – TreeAgePro output

Multivariate Analysis 1:

Variable value: Health effect from dual use	Variable value: Probability of combustible tobacco initiation - status quo	STRATEGY	Expected utility value
87	0.187	Ban on all flavored tobacco products	17.302531
87	0.17725	Ban on all flavored tobacco products	17.302531
87	0.1675	Ban on all flavored tobacco products	17.302531
87	0.15775	Ban on all flavored tobacco products	17.302531
87	0.148	Ban on all flavored tobacco products	17.302531
92.75	0.187	Ban on all flavored tobacco products	17.596264
92.75	0.17725	Ban on all flavored tobacco products	17.596264
92.75	0.1675	Ban on all flavored tobacco products	17.596264
92.75	0.15775	Ban on all flavored tobacco products	17.596264
92.75	0.148	Ban on all flavored tobacco products	17.596264
98.5	0.187	Ban on all flavored tobacco products	17.889997
98.5	0.17725	Ban on all flavored tobacco products	17.889997
98.5	0.1675	Ban on all flavored tobacco products	17.889997
98.5	0.15775	Ban on all flavored tobacco products	17.889997
98.5	0.148	Ban on all flavored tobacco products	17.889997
104.25	0.187	Ban on all flavored tobacco products	18.18373
104.25	0.17725	Ban on all flavored tobacco products	18.18373
104.25	0.1675	Ban on all flavored tobacco products	18.18373
104.25	0.15775	Ban on all flavored tobacco products	18.18373
104.25	0.148	Ban on all flavored tobacco products	18.18373
110	0.187	Ban on all flavored tobacco products	18.477463
110	0.17725	Ban on all flavored tobacco products	18.477463
110	0.1675	Ban on all flavored tobacco products	18.477463
110	0.15775	Ban on all flavored tobacco products	18.477463
110	0.148	Ban on all flavored tobacco products	18.477463
87	0.187	Ban on combustible flavored tobacco products	17.687953
87	0.17725	Ban on combustible flavored tobacco products	17.687953
87	0.1675	Ban on combustible flavored tobacco products	17.687953
87	0.15775	Ban on combustible flavored tobacco products	17.687953
87	0.148	Ban on combustible flavored tobacco products	17.687953
92.75	0.187	Ban on combustible flavored tobacco products	18.0076875
92.75	0.17725	Ban on combustible flavored tobacco products	18.0076875
92.75	0.1675	Ban on combustible flavored tobacco products	18.0076875
92.75	0.15775	Ban on combustible flavored tobacco products	18.0076875
92.75	0.148	Ban on combustible flavored tobacco products	18.0076875
98.5	0.187	Ban on combustible flavored tobacco products	18.327422
98.5	0.17725	Ban on combustible flavored tobacco products	18.327422
98.5	0.1675	Ban on combustible flavored tobacco products	18.327422
98.5	0.15775	Ban on combustible flavored tobacco products	18.327422
98.5	0.148	Ban on combustible flavored tobacco products	18.327422
104.25	0.187	Ban on combustible flavored tobacco products	18.6471565

104.25	0.17725	Ban on combustible flavored tobacco products	18.6471565
104.25	0.1675	Ban on combustible flavored tobacco products	18.6471565
104.25	0.15775	Ban on combustible flavored tobacco products	18.6471565
104.25	0.148	Ban on combustible flavored tobacco products	18.6471565
110	0.187	Ban on combustible flavored tobacco products	18.966891
110	0.17725	Ban on combustible flavored tobacco products	18.966891
110	0.1675	Ban on combustible flavored tobacco products	18.966891
110	0.15775	Ban on combustible flavored tobacco products	18.966891
110	0.148	Ban on combustible flavored tobacco products	18.966891
87	0.148	Status quo (no ban)	16.66022
92.75	0.148	Status quo (no ban)	16.950917
98.5	0.148	Status quo (no ban)	17.241614
87	0.15775	Status quo (no ban)	17.46017825
104.25	0.148	Status quo (no ban)	17.532311
92.75	0.15775	Status quo (no ban)	17.7582755
110	0.148	Status quo (no ban)	17.823008
98.5	0.15775	Status quo (no ban)	18.05637275
87	0.1675	Status quo (no ban)	18.2601365
104.25	0.15775	Status quo (no ban)	18.35447
92.75	0.1675	Status quo (no ban)	18.565634
110	0.15775	Status quo (no ban)	18.65256725
98.5	0.1675	Status quo (no ban)	18.8711315
87	0.17725	Status quo (no ban)	19.06009475
104.25	0.1675	Status quo (no ban)	19.176629
92.75	0.17725	Status quo (no ban)	19.3729925
110	0.1675	Status quo (no ban)	19.4821265
98.5	0.17725	Status quo (no ban)	19.68589025
87	0.187	Status quo (no ban)	19.860053
104.25	0.17725	Status quo (no ban)	19.998788
92.75	0.187	Status quo (no ban)	20.180351
110	0.17725	Status quo (no ban)	20.31168575
98.5	0.187	Status quo (no ban)	20.500649
104.25	0.187	Status quo (no ban)	20.820947
110	0.187	Status quo (no ban)	21.141245

Multivariate Analysis 2:

Variable value: Health effect from dual use	Variable value: Probability of ST initiation - status quo	STRATEGY	Expected utility value
87	0.113	Ban on all flavored tobacco products	17.302531
87	0.1045	Ban on all flavored tobacco products	17.302531
87	0.096	Ban on all flavored tobacco products	17.302531
87	0.0875	Ban on all flavored tobacco products	17.302531
87	0.079	Ban on all flavored tobacco products	17.302531
92.75	0.113	Ban on all flavored tobacco products	17.596264
92.75	0.1045	Ban on all flavored tobacco products	17.596264
92.75	0.096	Ban on all flavored tobacco products	17.596264
92.75	0.0875	Ban on all flavored tobacco products	17.596264

92.75	0.079	Ban on all flavored tobacco products	17.596264
98.5	0.113	Ban on all flavored tobacco products	17.889997
98.5	0.1045	Ban on all flavored tobacco products	17.889997
98.5	0.096	Ban on all flavored tobacco products	17.889997
98.5	0.0875	Ban on all flavored tobacco products	17.889997
98.5	0.079	Ban on all flavored tobacco products	17.889997
104.25	0.113	Ban on all flavored tobacco products	18.18373
104.25	0.1045	Ban on all flavored tobacco products	18.18373
104.25	0.096	Ban on all flavored tobacco products	18.18373
104.25	0.0875	Ban on all flavored tobacco products	18.18373
104.25	0.079	Ban on all flavored tobacco products	18.18373
110	0.113	Ban on all flavored tobacco products	18.477463
110	0.1045	Ban on all flavored tobacco products	18.477463
110	0.096	Ban on all flavored tobacco products	18.477463
110	0.0875	Ban on all flavored tobacco products	18.477463
110	0.079	Ban on all flavored tobacco products	18.477463
87	0.113	Ban on combustible flavored tobacco products	17.687953
87	0.1045	Ban on combustible flavored tobacco products	17.687953
87	0.096	Ban on combustible flavored tobacco products	17.687953
87	0.0875	Ban on combustible flavored tobacco products	17.687953
87	0.079	Ban on combustible flavored tobacco products	17.687953
92.75	0.113	Ban on combustible flavored tobacco products	18.0076875
92.75	0.1045	Ban on combustible flavored tobacco products	18.0076875
92.75	0.096	Ban on combustible flavored tobacco products	18.0076875
92.75	0.0875	Ban on combustible flavored tobacco products	18.0076875
92.75	0.079	Ban on combustible flavored tobacco products	18.0076875
98.5	0.113	Ban on combustible flavored tobacco products	18.327422
98.5	0.1045	Ban on combustible flavored tobacco products	18.327422
98.5	0.096	Ban on combustible flavored tobacco products	18.327422
98.5	0.0875	Ban on combustible flavored tobacco products	18.327422
98.5	0.079	Ban on combustible flavored tobacco products	18.327422
104.25	0.113	Ban on combustible flavored tobacco products	18.6471565
104.25	0.1045	Ban on combustible flavored tobacco products	18.6471565
104.25	0.096	Ban on combustible flavored tobacco products	18.6471565
104.25	0.0875	Ban on combustible flavored tobacco products	18.6471565
104.25	0.079	Ban on combustible flavored tobacco products	18.6471565
110	0.113	Ban on combustible flavored tobacco products	18.966891
110	0.1045	Ban on combustible flavored tobacco products	18.966891
110	0.096	Ban on combustible flavored tobacco products	18.966891
110	0.0875	Ban on combustible flavored tobacco products	18.966891
110	0.079	Ban on combustible flavored tobacco products	18.966891
87	0.079	Status quo (no ban)	17.498273
92.75	0.079	Status quo (no ban)	17.7749285
87	0.0875	Status quo (no ban)	17.906749
98.5	0.079	Status quo (no ban)	18.051584
92.75	0.0875	Status quo (no ban)	18.19953325
87	0.096	Status quo (no ban)	18.315225
104.25	0.079	Status quo (no ban)	18.3282395
98.5	0.0875	Status quo (no ban)	18.4923175
110	0.079	Status quo (no ban)	18.604895
92.75	0.096	Status quo (no ban)	18.624138

87	0.1045	Status quo (no ban)	18.723701
104.25	0.0875	Status quo (no ban)	18.78510175
98.5	0.096	Status quo (no ban)	18.933051
92.75	0.1045	Status quo (no ban)	19.04874275
110	0.0875	Status quo (no ban)	19.077886
87	0.113	Status quo (no ban)	19.132177
104.25	0.096	Status quo (no ban)	19.241964
98.5	0.1045	Status quo (no ban)	19.3737845
92.75	0.113	Status quo (no ban)	19.4733475
110	0.096	Status quo (no ban)	19.550877
104.25	0.1045	Status quo (no ban)	19.69882625
98.5	0.113	Status quo (no ban)	19.814518
110	0.1045	Status quo (no ban)	20.023868
104.25	0.113	Status quo (no ban)	20.1556885
110	0.113	Status quo (no ban)	20.496859

Multivariate Analysis 3:

Variable value: Probability of combustible tobacco initiation - status quo	Variable value: Probability of ST initiation - status quo	STRATEGY	Expected utility value
0.187	0.113	Ban on all flavored tobacco products	17.966623
0.187	0.1045	Ban on all flavored tobacco products	17.966623
0.187	0.096	Ban on all flavored tobacco products	17.966623
0.187	0.0875	Ban on all flavored tobacco products	17.966623
0.187	0.079	Ban on all flavored tobacco products	17.966623
0.17725	0.113	Ban on all flavored tobacco products	17.966623
0.17725	0.1045	Ban on all flavored tobacco products	17.966623
0.17725	0.096	Ban on all flavored tobacco products	17.966623
0.17725	0.0875	Ban on all flavored tobacco products	17.966623
0.17725	0.079	Ban on all flavored tobacco products	17.966623
0.1675	0.113	Ban on all flavored tobacco products	17.966623
0.1675	0.1045	Ban on all flavored tobacco products	17.966623
0.1675	0.096	Ban on all flavored tobacco products	17.966623
0.1675	0.0875	Ban on all flavored tobacco products	17.966623
0.1675	0.079	Ban on all flavored tobacco products	17.966623
0.15775	0.113	Ban on all flavored tobacco products	17.966623
0.15775	0.1045	Ban on all flavored tobacco products	17.966623
0.15775	0.096	Ban on all flavored tobacco products	17.966623
0.15775	0.0875	Ban on all flavored tobacco products	17.966623
0.15775	0.079	Ban on all flavored tobacco products	17.966623
0.148	0.113	Ban on all flavored tobacco products	17.966623
0.148	0.1045	Ban on all flavored tobacco products	17.966623
0.148	0.096	Ban on all flavored tobacco products	17.966623
0.148	0.0875	Ban on all flavored tobacco products	17.966623

0.148	0.079	Ban on all flavored tobacco products	17.966623
0.187	0.113	Ban on combustible flavored tobacco products	18.410831
0.187	0.1045	Ban on combustible flavored tobacco products	18.410831
0.187	0.096	Ban on combustible flavored tobacco products	18.410831
0.187	0.0875	Ban on combustible flavored tobacco products	18.410831
0.187	0.079	Ban on combustible flavored tobacco products	18.410831
0.17725	0.113	Ban on combustible flavored tobacco products	18.410831
0.17725	0.1045	Ban on combustible flavored tobacco products	18.410831
0.17725	0.096	Ban on combustible flavored tobacco products	18.410831
0.17725	0.0875	Ban on combustible flavored tobacco products	18.410831
0.17725	0.079	Ban on combustible flavored tobacco products	18.410831
0.1675	0.113	Ban on combustible flavored tobacco products	18.410831
0.1675	0.1045	Ban on combustible flavored tobacco products	18.410831
0.1675	0.096	Ban on combustible flavored tobacco products	18.410831
0.1675	0.0875	Ban on combustible flavored tobacco products	18.410831
0.1675	0.079	Ban on combustible flavored tobacco products	18.410831
0.15775	0.113	Ban on combustible flavored tobacco products	18.410831
0.15775	0.1045	Ban on combustible flavored tobacco products	18.410831
0.15775	0.096	Ban on combustible flavored tobacco products	18.410831
0.15775	0.0875	Ban on combustible flavored tobacco products	18.410831
0.15775	0.079	Ban on combustible flavored tobacco products	18.410831
0.148	0.113	Ban on combustible flavored tobacco products	18.410831
0.148	0.1045	Ban on combustible flavored tobacco products	18.410831
0.148	0.096	Ban on combustible flavored tobacco products	18.410831
0.148	0.0875	Ban on combustible flavored tobacco products	18.410831
0.148	0.079	Ban on combustible flavored tobacco products	18.410831
0.148	0.079	Status quo (no ban)	16.532258
0.148	0.0875	Status quo (no ban)	16.977199
0.15775	0.079	Status quo (no ban)	17.34894725
0.148	0.096	Status quo (no ban)	17.42214
0.15775	0.0875	Status quo (no ban)	17.79388825
0.148	0.1045	Status quo (no ban)	17.867081
0.1675	0.079	Status quo (no ban)	18.1656365
0.15775	0.096	Status quo (no ban)	18.23882925
0.148	0.113	Status quo (no ban)	18.312022
0.1675	0.0875	Status quo (no ban)	18.6105775
0.15775	0.1045	Status quo (no ban)	18.68377025
0.17725	0.079	Status quo (no ban)	18.98232575
0.1675	0.096	Status quo (no ban)	19.0555185
0.15775	0.113	Status quo (no ban)	19.12871125
0.17725	0.0875	Status quo (no ban)	19.42726675
0.1675	0.1045	Status quo (no ban)	19.5004595
0.187	0.079	Status quo (no ban)	19.799015
0.17725	0.096	Status quo (no ban)	19.87220775
0.1675	0.113	Status quo (no ban)	19.9454005
0.187	0.0875	Status quo (no ban)	20.243956
0.17725	0.1045	Status quo (no ban)	20.31714875
0.187	0.096	Status quo (no ban)	20.688897
0.17725	0.113	Status quo (no ban)	20.76208975
0.187	0.1045	Status quo (no ban)	21.133838
0.187	0.113	Status quo (no ban)	21.578779

Chapter 5 - Setting Performance Standards for FDA Policies: The Economic Impact of Regulating Flavored Tobacco Products

ABSTRACT

Introduction: The goals of this study were to determine acceptable ceiling costs for two policies that the FDA might consider to regulate the sale of flavored tobacco products in the United States, and to identify the minimum effectiveness standards at which these interventions would be considered cost-effective and cost-saving.

Methods: Using a cost-utility analytic framework, we employed threshold analyses to establish cost and performance standards for two regulatory options: 1) a ban on the sale of flavored combustible tobacco products, and 2) a ban on the sale of all flavored tobacco products. We used a previously developed mathematical model to estimate the reduction in the number of adult smokers expected to occur 15 years after the implementation of each policy. We conducted sensitivity analyses to examine the results given pessimistic and optimistic parameter assumptions.

Results: The maximum acceptable costs for a ban on the sale of flavored combustible tobacco products and a ban on the sale of all flavored tobacco products were calculated to be $18.7 ($16.2-$104.8) billion and $35.5 ($15.3–$337.2) billion, respectively. These values were substantially higher than the anticipated costs of the policies. We estimated that a ban on the sale of flavored combustible tobacco products would be cost-effective if 217 (21–1,280) adult smokers were averted, and a ban on the sale of all flavored tobacco products would be cost-effective if 266 (6–1,580) adult smokers were averted. These threshold values were substantially lower than the expected number of adult smokers

expected to be averted as a result of these policies: we found that a ban on the sale of flavored combustible tobacco products and a ban on the sale of all flavored tobacco products would avert 357,185 (336,351–378,166) and 676,223 (316,397–1,216,879) adult smokers, respectively. Both policies were found to be cost-saving given optimistic parameter assumptions.

Conclusions: The results of this study provide support for enacting either regulatory option considered. These results are limited by uncertain parameter values.

INTRODUCTION

The 2009 Family Smoking Prevention and Tobacco Control Act banned the sale of flavored cigarettes, excluding menthol (1). In April 2014, the U.S. Food and Drug Administration (FDA) published a proposed ruling in which it requested research and data to support the extension of the flavored cigarette ban to non-cigarette tobacco products (2).

In its proposed ruling, the FDA acknowledged the unique role that flavored tobacco products may play in facilitating tobacco use among young populations, noting that "many of the products proposed to be covered by this rule are offered in fruit and candy flavors, such as chocolate and grape flavors, making them especially attractive to children and young adults" (3). Further, in its request for comments on approaches to regulate flavored tobacco, the FDAs specifies that polices should "address the sale of candy and/or fruit-flavored tobacco products to children and young adults" (3). Indeed, qualitative data suggests that flavoring may drive tobacco use in adolescent and young

adult populations (4-6), and survey data shows that the prevalence of flavored tobacco use in higher in youth and young adults when compared to older adult populations (7, 8). National data from the Legacy Young Adult Cohort Study indicate that in 2011,18.5% (95% CI: 15.2-22.2) of young adults aged 18-34 who reported past 30-day use of any tobacco product used a flavored product (9).

Given the FDA's interest in regulating non-cigarette flavored tobacco products, the goals of this paper were to determine acceptable ceiling costs for two policies that the FDA might consider to regulate the sale of flavored tobacco products, and to identify the minimum effectiveness standards at which these policies would be considered cost-effective and cost-saving. We established cost and performance standards for two regulatory options: 1) a ban on the sale of all flavored combustible tobacco products, and 2) a ban on the sale of all flavored tobacco products (inclusive of combustible and smokeless products).

METHODS

Using a cost-utility analytic framework, we employed threshold analyses to establish cost and performance standards for the two regulatory options described above. We chose this framework because the outputs of a cost-utility analysis are typically expressed in quality-adjusted life years (QALYs). This type of measure is useful because it accounts for both morbidity and mortality, and allows for comparisons across other types of interventions (10).

We performed sensitivity analyses to examine the results given pessimistic and optimistic parameter assumptions. Per standard practice, Quality Adjusted Life Years (QALYs) were discounted at 3% (11, 12). This analysis employs a societal perspective and presents all costs in 2013 U.S. dollars. We used Microsoft Excel 2011 to conduct this analysis.

Most of the existing data on the costs of tobacco use and benefits of cessation have been estimated exclusively for cigarette smokers (13, 14). Thus, unless otherwise noted, the estimates for the costs of tobacco use and benefits of cessation employed in this analysis are cigarette-specific.

Parameter definitions

For this study, a "case" was defined as an individual aged 35 who continues to smoke combustible tobacco products until death. Combustible tobacco users included those who use combustible products exclusively, as well as dual users of combustible and smokeless products.

We defined the following parameters as follows:

- A = number of reduced cases expected 15 years after the implementation of the policy, compared to a scenario in which no additional flavor tobacco product bans have been enacted
- Q = QALYs saved when a case is averted
- W = amount society is willing to pay per one QALY
- T = medical treatment costs saved per case averted

C = cost of implementing the policy

Analytic approach

In order to determine the upper limit cost at which society would be willing to pay for the implementation of each policy, we solved for the parameter C such that:

$$C = W(AQ) + AT$$

The cost-effectiveness threshold, which is defined as the number of cases that would need to be averted for the policy to be considered cost-effective, was calculated using the equation:

$$A = C/(T+(Q*W))$$

To calculate the cost-saving threshold, which is defined as the number of cases that would need to be averted for the policy to be considered cost-saving, we solved for A using the equation:

$$A = C/T$$

We chose to conduct analyses to establish both acceptable upper limit costs and minimum effectiveness standards in order to address the uncertainty involved in quantifying the costs and benefits of the policies under consideration. That is, in order to

solve for the parameter *C*, we must estimate the value for the parameter *A*. Likewise, to solve for the parameter *A*, we must estimate the value for the parameter *C*. As discussed in depth below, the values for the parameters *C* and *A* were subject to uncertainty. Thus, we conducted analyses to determine both acceptable upper limit costs and minimum effectiveness standards for the policies in order to bolster confidence in recommendations to the FDA that arise as a result of this study. That is to say, the evidence supporting a recommendation to implement one or either policy is strengthened if the results of both analytic approaches support identical conclusions.

Parameter Estimates

A summary of the parameter values can be found in **Table 5-1**.

Reduction in the number of cases expected 15 years after policy implementation (A)

We calculated the cases averted for each policy scenario using the decision tree previously described. We applied the decision tree probabilities to a cohort of 73,359,000, representing the U.S. Census Bureau's 2012 estimate of the number of 18-34 year olds in the United States (15). We estimated the incremental values for *A*, when compared to the status quo, by calculating the difference between the number of combustible-only users and dual users (combustible and smokeless) under the policy and status quo scenarios. This analysis did not consider individuals who use smokeless tobacco exclusively to be "cases."

QALYs saved when a case is averted (Q)

Using data published by Cromwell et al. for 25-29 year olds (16), Wang et al. estimated that 1.05 QALYs, discounted at 3%, are saved for each established smoker prevented (12). Per Cromwell et al.'s estimates, this calculation assumes a 45% rate of smoking relapse. This is a conservative estimate for the present analysis, because the individuals in this analysis are older than 25-29. Javtiz et al. calculated the QALYs saved when quitting occurs between the ages of 30-39 and found that, undiscounted, 7.14 QALYs were saved for men and 5.96 QALYs were saved per woman. Discounted at 3%, and assuming that men smoke 1.3 times as much as women, we estimated that 2.32 QALYs are saved per case averted in the optimistic scenario of the sensitivity analysis. This value assumes 1.5% yearly spontaneous quit rate, and a 37% lifetime relapse rate. Other tobacco studies have employed these values (17).

Society's willingness to pay for one QALY (W)

Cost-effectiveness analyses conducted in the United States typically employ $50,000 per QALY as the estimate for *W*, although the origins of this value are unclear (18). This value is not updated regularly to adjust for inflation, and the scientific merit of using this benchmark for present-day analyses has been debated (19). In 2008, Braithwaite et al. (19) published a study in which they derived updated values for *W*. The authors of this study concluded that the lower and upper range for *W* should be $109,000-$297,000 per QALY saved.

In this analysis, we used a value of $50,000 per QALY in the base case analysis. Employing this estimate facilitates comparisons between the results of this analysis and other studies that have employed this value. We used Braithwaite et al.'s updated value of $109,000 for the optimistic scenario in the sensitivity analysis.

Medical treatment costs saved per case averted (T)

The parameter T is the net present value of lifetime medical treatment costs saved per quit, discounted at 3%. According to an analysis conducted by Hodgson, when adjusting for mortality, smokers spend less than nonsmokers over the lifetime on medical expenditures (20). This occurs because former smokers live longer and incur more medical costs due to survival beyond continuing smokers. However, monetarily valuing death over life in the base case scenario does not reflect the societal goal of prolonging life. To manage this dilemma, tobacco economic evaluations have employed a value of $0 to estimate *T* (17, 21). We employ this value of $0 in the base case scenario in this analysis.

The pessimistic scenario reflects the notion that smokers may spend less than nonsmokers on medical care over the lifetime. For the pessimistic scenario, we estimated *T* at -$4,253 (2013 dollars, discounted at 3%), based on an adjustment to Warner et al.'s estimation of the additional medical costs that smokers who quit incur, as compared to continuing smokers (22).

For the optimistic scenario, we employed a value based on Hodgson's estimate that male smokers spend $8,638 more on medical costs than male non-smokers, and female smokers spend $10,119 more on medical costs than female nonsmokers (1990 dollars, discounted at 3%) (20). Using the medical care component of the Consumer Price Index to convert these values to 2013 dollars, we estimated that male smokers spend $26,424 more on medical costs than male non-smokers, and females spend $10,119 more on medical costs than female nonsmokers (23). Taking into account an estimate that the number of young adult males who smoke is approximately 1.3 times that of females (24), we estimated that, across both genders, smokers spend approximately $24,240 more than nonsmokers on medical costs. Related literature has employed this approach to estimating this parameter for base case and optimistic case scenarios (11).

Cost of the intervention (C)

Despite the passage of the 2009 ban on flavored cigarettes, as well as the implementation of additional flavored product bans in New York City, Maine and elsewhere (25), we were unable to locate an estimate of the cost of implementing a ban on flavored tobacco products in a search of publically available local-level and federal documents. Thus, we estimated *C* based on FDA calculations of other tobacco control policies.

The FDA recently published a Regulatory Impact Analysis (RIA) to assess the economic impact of extending regulations that currently apply to cigarettes, cigarette tobacco, roll-your-own-tobacco, and smokeless tobacco to other types of tobacco products (13). These

regulations include those requiring product registration, disclosure of ingredients, product labeling, identification requirements, and warning statements for packages (13).

In the RIA, the FDA considered two scenario – one in which all cigars (including premium cigars), pipe tobacco, hookah tobacco, electronic cigarettes and other novel tobacco products would be subject to current regulations, and one in which premium cigars would be exempt from these regulations (13). For each scenario, the FDA provided base case, lower bound and upper bound estimates of the upfront and annual costs (13). The FDA included costs to the tobacco industry in its estimates, as well as costs to the FDA. The costs to the industry included costs to comply with the FDA's regulations, as well as other types of costs, such as expenditures for point-of-sale advertising.

We used the FDA cost estimates for the policy scenarios examined in the RIA as a guide to obtain a reasonable range of values for the parameter *C*. We assumed that the cost of implementing the policies examined the RIA would be significantly higher than those for the policies considered in the present analysis. The primary costs of implementing a ban on flavored tobacco products would likely occur in the form of lost revenue to the industry, as well as administrative and enforcement costs to the FDA. Administrative costs for a ban on flavored tobacco products would be lower than those incurred for the policies examined in the RIA, as the RIA states that the a considerable portion of the administrative costs to the FDA would emerge as a result of reviewing new product submissions.

We estimated base case, pessimistic and optimistic costs for the two policies considered in this analysis. We derived costs for a ban on all flavored tobacco products from the scenario, as described in the RIA, in which premium cigars were included in the analysis. We derived costs for a ban on combustible flavored tobacco products from the scenario in which premium cigars were excluded from the analysis. In our calculation of the optimistic estimate for *C*, we excluded costs to the industry. The pessimistic estimate of *C* included the value estimated by the FDA to market new tobacco products; other costs to the industry were not included, as they are not applicable for a product ban. The base case estimate for *C* included half of the undiscounted upfront primary cost to the FDA; we assumed that the costs of flavored tobacco bans would be incurred only in the short term and, thus, the annual costs were not included. The pessimistic estimates include only the undiscounted base case costs to the FDA. We used the undiscounted costs in this analysis in order to be as conservative as possible in estimating the costs, and because costs are assumed to be spent immediately.

Table 5-1. Parameter values

Parameter	Base Case Estimate	Sensitivity Estimates	Sources
A Reduction in the number of adult smokers expected as a result of a ban on combustible flavored products, compared to the status quo	357,185	(336,351–378,166)	Author's calculation
A Reduction in the number of adult smokers expected as a result of a ban on all flavored products, compared to the status quo	676,223	(316,397–1,216,879)	Author's calculation
T Medical treatment costs saved per case averted	$0	(-$4,253 - $24,240)	(11, 17, 20-22)
Q QALYs saved when a case is averted	1.05	(1.05-2.32)	(12, 16, 17, 26)
W The amount society is willing to pay for one QALY	$50,000	$109,000	(18, 19)
C Cost of implementing a ban on combustible flavored products	$11,380,000	($5,690,000-$61,760,000)	(13)
C Cost of implementing a ban on all flavored products	$13,970,000	($1,590,000-$76,210,000)	(13)

RESULTS

When compared to a scenario in which no additional flavored tobacco product bans have been implemented, we estimated that a ban on the sale of flavored combustible tobacco products would avert 357,185 (336,351–378,166) adult smokers, and a ban on the sale of all flavored tobacco products would avert 676,223 (316,397–1,216,879) adult smokers. These estimates capture the number of adult smokers averted 15 years after the implementation of the policies. These estimates assume that individuals have quit combustible tobacco by age 35 and do not relapse over their lifetime.

The results of the cost threshold analysis can be found in **Table 5-2**. The maximum acceptable costs for a ban on the sale of flavored combustible tobacco products and a ban on all flavored tobacco products were calculated to be approximately $18.7 ($16.2-$104.8) billion and $35.5 ($15.3–$337.2) billion, respectively. The wide ranges of possible values reflect uncertainty in the parameter estimates. However, the results of the sensitivity analysis indicated that, even given worst-case assumptions for all parameter estimates, spending for these interventions would need to reach well over a billion dollars in order for costs to extend beyond an acceptable amount. The pessimistic threshold value for a ban on all flavored tobacco products was calculated to be $15,265,206,059 in 2013 dollars; this was the lowest threshold value estimated for either policy. Thus, even though the sensitivity analysis produced wide ranges as results, the results were consistent with regard to the scale (billions of dollars) that would need to be spent in order for the cost of either policy to be considered socially unacceptable.

Table 5-2. Results of the cost threshold analysis

Scenario	Expected cost for the policy	Acceptable cost for the policy	Difference between expected cost and acceptable cost for the policy
Ban on combustible flavored products			
Base Case	$11,380,000	$18,752,212,500	$18,740,832,500
Pessimistic Case	$61,760,000	$16,227,926,697	$16,166,166,697
Optimistic Case	$5,690,000	$104,797,361,920	$104,791,671,920
Ban on all flavored products			
Base Case	$13,970,000	$35,501,707,500	$35,487,737,500
Pessimistic Case	$76,210,000	$15,265,206,059	$15,188,996,059
Optimistic Case	$1,590,000	$337,221,508,480	$337,219,918,480

The results of the cost-saving and cost-effectiveness threshold analyses can be found in **Table 5-3.** We do not report the results of the pessimistic-case scenarios for the cost-saving threshold analyses because, by definition, the results represent the number of individuals who would need to continue smoking in order to make the policies cost-saving. Given that the goal of the policies is to reduce smoking-related morbidity and mortality, this value is not relevant. Both policies are cost-saving only under the optimistic scenarios. The results of the cost-effectiveness threshold analysis indicate that, using pessimistic scenario values (the most conservative values), both policy options are cost effective if less than 1% of the expected number of averted cases is actually averted.

Table 5-3. Results of the cost-saving and cost-effectiveness threshold analyses

Scenario	Expected number of smokers averted (*A*)	Reduction in number of smokers need to meet cost-saving threshold	Reduction in number of smokers needed to meet cost-effectiveness threshold
Ban on combustible flavored products			
Base Case	357,185	~11,380,000,000	217
Pessimistic Case	378,166	X	1,280
Optimistic Case	336,351	235	21
Ban on all flavored products			
Base Case	676,223	~13,970,000,000	266
Pessimistic Case	1,216,879	X	1,580
Optimistic Case	316,397	66	6

DISCUSSION

We estimated that the upper limit cost at which society would enact a ban on combustible flavored products was approximately $18.8 billion ($16.2 -$104.8 billion), and the upper limit cost at which society would enact a ban on all flavored products was approximately 35.5 billion ($15.3 - $337.2). Using conservative values for the cost of these interventions, approximately 217 (21 – 1,280) individuals would need to quit combustible tobacco use by the age of 35 in order for a ban on combustible flavored products to be considered cost-effective, and approximately 266 (6 - 1,580) individuals would need to quit combustible tobacco use by the age of 35 in order for a ban on all flavored tobacco products to be considered cost-effective. Because we intentionally biased the value for the parameter *T* to acknowledge the increased medical costs of smoking cessation over smoking-attributable death, the cost-saving results did not favor these policies.

The results of this study suggest that, from an economic perspective, it is reasonable for the FDA to implement either of the policies examined in this analysis. Even considering

uncertainty in the parameter values, the data indicate that the cost of both policies are likely to meet acceptable spending standards, and both policies likely represent cost-effective approaches to reducing tobacco use in the United States. While a ban on all flavored tobacco products generated more favorable results than a ban on combustible flavored tobacco products, the uncertainty inherent in the parameters *A* and *C*, perhaps, weakens our ability to confidently recommend one policy approach over the other. The evidence supporting the implementation of either of the bans, as opposed to implementing no additional ban, however, is robust.

The results of this analysis are limited by uncertainty in the parameter values. We discussed the limitations of the decision tree used to generate the cases averted by these polices in a previous paper. As noted in comments on the FDA's RIA, estimates for the medical treatment costs saved per case averted need to be updated to reflect current tobacco use and health care use patterns (14). We estimated cost values by using the total estimated cost for other FDA interventions as ballpark benchmark values; this approach, while likely conservative, should be quantified directly by bodies implementing relevant flavored tobacco regulations in order to obtain a more accurate estimate. Additionally, we drew upon literature for the values for parameters *Q* and *T* that was specific to cigarettes. Future studies should investigate how the values for these parameter values might differ for other combustible and noncombustible products. With product-specific information on the costs and outcomes of tobacco use, we would be able to better estimate the effects of policies that target certain products. In the face of these limitations, we aimed to provide a conservative analysis. These analyses provide a framework for future studies; the results can be updated as more accurate and current data become available.

These results provide support for policies that decrease smoking prevalence among young adults. Developing tobacco control policies specifically for young adults appears to be a cost-effective strategy to reduce the economic and health burden inflicted by tobacco use in the U.S., assuming that the cost of such policies are not too high. That said, banning some or all flavored tobacco products would not resolve the tobacco epidemic. The regulatory options explored in this paper could be combined with other interventions aimed at reducing tobacco initiation and increasing cessation in this population in order to maximize the effectiveness of tobacco control policies.

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Chapter 6 – INTEGRATION OF STUDY FINDINGS

INTRODUCTION

The purpose of this dissertation was to synthesize and translate research on flavored tobacco in the U.S. in order to inform regulatory decision-making at the U.S. Food and Drug Administration (FDA). The three related manuscripts presented in this dissertation provide an overview of how researchers have investigated the use and attitudes/knowledge/perception of flavored tobacco products; explore the potential health effects of implementing flavored tobacco product bans beyond the 2009 Family Smoking Prevention and Tobacco Control Act's (FSPTCA's) policy restricting the sale of flavored cigarettes; and establish cost and performance standards for potential policy approaches to regulate flavored tobacco products. This chapter summarizes the findings from those three manuscripts, and provides a general discussion on the strengths, limitations, and future directions of this research.

SUMMARY OF RESULTS

The first manuscript in this dissertation described a systematic review that provided an overview of research examining the use and attitudes/knowledge/perception of flavored tobacco use in the U.S., specifically focusing on how age and nonflavored tobacco use are correlated with flavored tobacco use. The results of the review found that young age was associated with flavored tobacco use, and that flavoring in tobacco products is an

attractive trait for adolescent and young adult populations. The literature was inconclusive with regard to how flavored tobacco might facilitate tobacco initiation. Flavored tobacco use may be associated with dual use of other tobacco products. These findings represent a synthesis of data from 32 studies that exhibited a high level of heterogeneity with regard to their research questions, study designs, populations investigated and measures used.

The results of the systematic review suggest that the field would benefit from additional research investigating the use and attitudes/knowledge/perception of flavored tobacco. Valid and reliable measures to investigate these concepts should be standardized to facilitate meta-analyses of multiple studies, and longitudinal data should be collected in order to track patterns of tobacco use in a generalizable population. Such data would provide evidence that more directly speaks to questions about the impact of flavored tobacco use on tobacco initiation, switching between products, dual use, and cessation.

The second manuscript employed a decision tree to estimate the relative health effects, compared to the status quo, that would be expected to result from a) a ban on combustible flavored tobacco products and b) a ban on all flavored tobacco products. Given the model's underlying structural and parameter assumptions, the decision tree found that a ban on all flavored tobacco products would likely produce the most favorable outcome of the policy options considered. The sensitivity analysis highlighted parameters that contributed to the majority of the uncertainty in the model: 1) the probability of combustible tobacco initiation under the status quo, 2) the probability of smokeless

tobacco initiation under the status quo, and 3) the health effect associated with dual (combustible/smokeless) tobacco use.

The uncertainty represented by the first two parameters described above speaks to a need to monitor patterns of tobacco use more closely in order to gain a better understanding of the types of products with which non-users initiate tobacco and how their patterns of tobacco use change over time. The uncertainty represented by the third parameter – the health effect associated with dual tobacco use – points more specifically to a need to understand how adding, promoting or banning certain products within the tobacco marketplace may impact exposure to harm. Understanding the dynamics of these types of changes to the marketplace would provide insight into the extent that policymakers can reduce tobacco-induced harm by manipulating the products available to potential and current tobacco users.

In the third manuscript, we used threshold analyses to determine acceptable ceiling costs for the policies considered in the second manuscript, and to identify the minimum effectiveness standards at which these interventions would be considered cost-effective and cost-saving. We employed conservative parameters for both analyses. The results of the cost threshold analysis found that the cost of either ban would need to reach well into the multi-billion dollar range in order for society to deem the cost of either of the policies to be unacceptable. The results of the cost-saving threshold analysis were only cost-saving under the optimistic scenarios examined, because we intentionally biased the analyses to consider the additional medical costs that former smokers incur beyond those

of continuing smokers, who have shorter life expectancies than former smokers. The results of the cost-effectiveness threshold analysis show that both policy options would be cost-effective if less than 1% of the expected number of averted cases is actually averted.

The results of these threshold analyses provide support, from an economic perspective, for banning combustible flavored tobacco products or all flavored tobacco products. These results are limited by uncertain parameter values with regard to the expected costs and effects of these policies, as well as potentially outdated values for the medical costs averted by quitting tobacco. Current estimates for the medical costs averted as a result of quitting tobacco were estimated at least a decade ago (1, 2). Additionally, these estimates are smoking-specific, and do not include the costs incurred by smokeless tobacco use.

Taken together, the results of these three manuscripts found that the effects of a flavored tobacco product ban would likely reduce tobacco initiation among young adults, which would result in improved health at the population level. Uncertainty in quantifying the costs and effects of the two product bans under consideration, perhaps, weakens our ability to confidently recommend one approach over the other. However, the evidence supporting the implementation of either ban, as opposed to implementing no additional ban, is robust.

DISCUSSION OF FINDINGS

The development, execution and findings of this dissertation reflect the dynamics described in Holtgrave's three-box model (3). The study questions and designs for the three manuscripts were conceptualized with the intention to inform FDA decision-making. The first manuscript synthesized existing research on the use and attitudes/knowledge/perceptions of flavored tobacco products, and the subsequent manuscripts employed these findings to evaluate potential approaches to regulating the sale of flavored tobacco products in the U.S. The results of these studies provide data that are relevant to FDA interests and, by highlighting weaknesses and gaps in existing literature, they present questions that could be investigated in future research projects.

While the results of this dissertation speak to FDA interests, limitations of the research should be considered when assessing the applicability of these findings to policy-making. The eligibility criteria for the systematic review were limited to studies that assessed the use and/or attitudes/knowledge/perception of flavored tobacco products. These criteria were developed in consultation with tobacco researchers and were chosen, in part, because it was thought that existing literature would benefit from being synthesized and assessed for quality. While the systematic review was successful in achieving these tasks, the review's relevancy to the FDA's questions is perhaps not as strong as it could have been. For example, in the proposed ruling that it published in April 2014, the FDA asked, "What is the likelihood that individuals who engage in flavored tobacco product use will initiate cigarette use and/or become dual users with cigarettes?" (4). The degree to which the attitudes/knowledge/perception of flavored tobacco products impacts cigarette

initiation or dual use warrants further investigation. While this, perhaps, represents a drawback in the applicability of the results of the systematic review, the study exhibits strong internal validity.

While the second and third manuscripts address the limitation described above by asking questions that more directly speak to FDA requests for data, the models developed for these manuscripts are limited by uncertainty in their parameter values. This uncertainty reflects the type of data that is currently available to inform these models. The thorough description of the development of these models, however, which ensures the ability of other modelers to replicate the results, makes it possible for these models to be updated as relevant data is published. The construction of these models in the face of limited data is important, as the process highlights areas for future research. Indeed, "[i]f decision analyses were not used…there would still be uncertainty in the decision-making process. When decision analysis is used, the areas of uncertainty are clearly identified" (5). Along similar lines, these models may over-simplify tobacco use behaviors, as they do not take into account many of the complex factors that go into decisions to initiation, persist and quit tobacco use. Future models may build upon the ones developed for this dissertation and introduce complexities.

This dissertation aims to strengthen the relationship between science and policy in tobacco control; however, it is important to note the limits of this relationship. The findings presented in these manuscripts represent one of many considerations that decision-makers must take into account when enacting policies. The economic evaluation

performed in the third manuscript highlights the importance of those other considerations. Using a negative value to estimate the medical costs averted when an individual quits smoking – which reflects the longer life that former smokers are likely to have compared to continuing smokers – does not accurately represent the value that society and government place on prolonging life. This limitation is inherent in the economic evaluation. While other values can be used to estimate the parameter so that the results of the analysis do not promote mortality, using these values perhaps represents a lapse in "scientific" practices; the researcher's values explicitly impact the way in which the study is conducted. Acknowledging this does not suggest that economic evaluations similar to the one conducted for this dissertation should not be performed. Ignoring such nuances would weaken, rather than strengthen the linkage between science and policymaking. Rather, it emphasizes the limit of this methodology in its relation to informing this policy decision, and illustrates the need for decision-makers to think critically about enacting policies, even when the rationale for those policies are supported by scientific evidence.

The regulatory approaches examined in the second and third manuscripts – and, indeed, any policy targeted at flavored tobacco products – represent one of many potential policies that the FDA could consider to minimize the attractiveness of tobacco products and to make tobacco use less pleasurable. For example, the FDA might consider plain packaging requirements, implementing additional restrictions on marketing and advertising, or making adjustments to pH and nicotine levels in tobacco products. Indeed, the implementation of a ban on some or all flavored tobacco products would not

completely resolve the tobacco epidemic. The FDA should consider a flavored tobacco product ban along with other policies.

FUTURE DIRECTIONS AND RECOMMENTATIONS

The results of all three manuscripts highlighted the need for additional data to be collected to inform key questions about the harms that the sale of flavored tobacco products may present. Much of the available data employed in this dissertation was collected before new products, such as electronic cigarettes, were widely available and, thus, may not reflect current patterns of tobacco use. All three manuscripts would have benefited from the availability of longitudinal data that monitors tobacco initiation, switching behaviors, polytobacco use and cessation over time.

Given the plethora of tobacco and nicotine products that are currently available to consumers, future research investigating use of tobacco would be improved by employing questions that ask about use of these products as specifically as possible. For example, one paper included in the systematic review, conducted by Villanti et al. (6), queried participants about their use of flavored tobacco two times – one question specifically asked participants to exclude their use of menthol products, and one did not. Making this type of distinction is important, as the results of these questions differed from one another; some participants may have considered menthol to be a flavor. Bearing in mind the importance of differentiating between "flavored" and "menthol" in a policy context, it is important to develop data collection techniques that accurately reflect the specific products being used. This consideration should be applied to research on flavored

products, as well as to research on other products. Consumers of electronic cigarettes, for example, may refer to these products by names such as “vape pens” and “e-hookahs,” and consumers may differentiate between these products in ways that researchers do not.

Improvements in data collection would strengthen the models developed in the second and third manuscripts of this dissertation. While modeling techniques can be used to predict the outcomes of policies, their results are only as good as the data informing the model. The FDA has expressed interest in using mathematical modeling techniques to evaluate the population effects of its policies (7, 8). Thus, as better data is collected, these data should be applied to models that can help decision-makers evaluate the effects of potential regulatory approaches.

Even before improved data is collected, however, the model presented in the second manuscript can serve as an important tool for understanding a range of tobacco control issues. The model developed for this paper provided a framework for examining regulatory approaches intended to reduce the attractiveness of tobacco products, and it weighed the impact of reducing the attractiveness of some tobacco products but not others while taking into consideration the varying levels of risk that those products present. Thus, this model could be used to think about a range of policy issues, such a the potential impact of making products such as e-cigarettes or nicotine replacement therapy more or less attractive than other tobacco products.

In addition to the recommendations described above, future research may benefit from knowledge generated in studies conducted with non-U.S. samples. Lessons learned from policies enacted in other locations may be useful to inform decision-making in the U.S. Conversely, the findings of this dissertation – and findings from other studies conducted in the U.S. – may be valuable for researchers and policymakers working internationally.

CONCLUSION

This project synthesizes and translates the best available evidence to assess tobacco regulatory policies that the FDA may soon consider to regulate the sale of flavored tobacco products. The methodologies employed in this project are intended to be transparent, and to give a clear sense of what is known and what assumptions are being made to reach its conclusions. The framework developed for this analysis can be built upon and tweaked as better and more data is collected to inform the policy decision at hand. This project contributes to the growing field of systems sciences, as applied to public health problems.

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POSTERS AND PRESENTATIONS

1. **Feirman S**, Donaldson E, Pearson J, Zawistowski G, Niaura R, Villanti A. Simulation Modeling in Tobacco Control Research: A Systematic Review. Poster presented at the 2014 Annual Meeting for the Society for Research on Nicotine and Tobacco.
2. Pearson JL, **Feirman S**, Abrams D, Hassmiller Lich K. An Initial System Dynamics Model of the Effect of E-cigarettes on Current Smokers' Tobacco Use Behavior. Poster presented at the 2013 Annual Meeting for the American Academy of Health Behavior.
3. Cantrell J, Vallone D, Nagler R, Thrasher JF, **Feirman S**, Muenz LR, He DY, Viswanath V. Experimental Study of Text-only vs. Text+Graphic Cigarette Warning Labels Examined by Race/ethnicity and Education. Poster presented at the 2012 Annual Meeting for the American Academy of Health Behavior.

4. Blank D, **Feirman S**. Expanding Teen Club in Swaziland to Address the Challenges of HIV Stigma, Lessons Learned from Botswana. Oral presentation at the 2010 Baylor International Pediatric AIDS Initiative Network Meeting.

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